# NIAID

National Institute of Allergy and Infectious Diseases

# Profile

## Fiscal Year 2001

National Institute of Allergy and Infectious Diseases
NATIONAL INSTITUTES OF HEALTH

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This is a stylized representation of an antibody, a protein made by the body's immune system cells to protect it against invading foreign substances.

For additional information, see our web site at
www.niaid.nih.gov

# Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) supports and conducts research to better understand, treat, and prevent infectious, immunologic, and allergic diseases. The scope of the NIAID research portfolio is expanding continually in response to new challenges, such as the emergence of AIDS and other newly recognized diseases, and because of scientific opportunities facilitated by new technologies and progress in the core NIAID scientific disciplines of microbiology and immunology. Advances in these key fields, including progress in relatively new areas such as pathogen and human genomics, are driving the development of new treatments, vaccines, and diagnostic tests that improve the health of people in the United States and around the world.

To meet the many health challenges of the new millennium and to take advantage of unprecedented scientific opportunities, the Institute has developed a strategic research plan for the 21st century centered on four major areas: (1) global health and emerging infectious diseases, (2) HIV/AIDS, (3) immune-mediated diseases, including allergy and asthma, and (4) vaccines. The complete *NIAID Strategic Plan for Addressing Health Disparities* is available at www.niaid.nih.gov/strategicplan2000. NIAID recently supplemented this comprehensive strategic plan with a strategic plan on health disparities and a new global health research plan for HIV/AIDS, malaria, and tuberculosis, which outlines NIAID's goals and plans for fighting infectious diseases by building sustained research capability domestically and internationally and enhancing international partnerships.

NIAID has a long history of supporting research into diseases that transcend national boundaries and hence fall under the rubric of global health. Examples of such diseases include newly recognized conditions, such as liver disease caused by hepatitis C virus and AIDS; diseases that have spread to new geographic areas, such as West Nile fever and dengue; and resurgent endemic diseases, such as malaria and tuberculosis, which are increasingly resistant to antimicrobial drugs. In addition, we now face the specter of a new kind of emerging disease—one spread deliberately by bioterrorists. These emerging and reemerging diseases are superimposed on other major health problems, such as acute respiratory infections, diarrheal diseases, and measles, which remain leading causes of illness and death worldwide. To mitigate the burden of these diseases, NIAID supports numerous laboratory, field-based, and clinical research projects related to global health, both domestically and abroad.

Many of the challenges posed by infectious diseases lend themselves to research in a relatively new field—genomics. The genomic sequencing of microbial pathogens will be a critical component of 21st century strategies for the development of diagnostics, therapeutics, and vaccines for infectious diseases. NIAID has funded projects to sequence the genomes of more than 50 medically important pathogens, more than a dozen of which have been completed. In the interest of global scientific cooperation, NIAID-supported scientists deposit pathogen sequence data in specialized public databases that investigators around the world can access through the World Wide Web.

Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), has claimed 22 million lives since the disease was recognized 20 years ago. More than 40 million people are living with HIV infection, including approximately 800,000 to 900,000

individuals in the United States.[1] In the United States and other western countries, potent combinations of anti-HIV drugs (highly active antiretroviral therapy, or HAART) have dramatically reduced the numbers of new AIDS cases and AIDS deaths. NIAID-supported investigators conducted research that was pivotal to the development of these drugs and have helped define how best to use these medications in different clinical settings. Ongoing research promises to yield a new generation of drugs that may improve on existing medications in terms of cost, effectiveness, and tolerability. Moreover, progress toward an AIDS vaccine holds promise for the future ability to protect individuals from this dreaded disease.

Until recently, expensive HAART regimens were considered to be beyond the reach of developing countries, where 95 percent of the world's HIV-infected people live.[2] Now, with dramatic reductions in the price of antiretroviral drugs for developing nations and the commitment of world leaders to address the AIDS problem in southern Africa and other poor regions of the world, AIDS therapies will begin to reach more people in poor countries who can benefit from them. Building on the research infrastructure that NIAID has helped establish in Africa and elsewhere in the developing world, we intend to work with our international colleagues to link the provision of anti-HIV therapy to ongoing efforts in prevention research, with the goal of facilitating a comprehensive approach to the AIDS pandemic in poor countries.

Immunologic diseases cause a considerable burden of illness and death in the United States. Autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, also afflict the U.S. population. Asthma, a chronic lung disease, affects an estimated 17 million Americans, and each year nearly 500,000 Americans are hospitalized and more than 5,000 die from asthma.[3] In addition, immune-mediated graft rejection remains a significant obstacle to the successful transplantation of potentially life-saving organs.

NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals with these and other immunologic conditions. For example, researchers are developing novel ways of selectively blocking inappropriate or destructive immune responses while leaving protective immune responses intact. This approach, called tolerance induction, holds great promise for the treatment of many immune-mediated conditions, including autoimmune diseases and asthma and allergic diseases. The Institute's most prominent effort in the field of immune tolerance is the Immune Tolerance Network (ITN), an international consortium of more than 70 research groups. The ITN is implementing clinical trials in four areas: transplantation of islets (the insulin-producing cells of the pancreas), kidney transplantation, autoimmune diseases, and asthma and allergic diseases.

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[1] UNAIDS. *Report on the global HIV/AIDS epidemic,* December 2001; Centers for Disease Control and Prevention. *HIV/AIDS surveillance report* 2000.

[2] UNAIDS. *Report on the global HIV/AIDS epidemic,* December 2001.

[3] www.niaid.nih.gov/newsroom/focuson/asthma01.

For more than a decade, NIAID has worked to reduce the burden of asthma, particularly among inner-city children. Investigators of NIAID's National Cooperative Inner-City Asthma Study developed a successful behavior and education intervention that substantially reduced asthma severity in these pediatric populations. Building on this success, NIAID and the Centers for Disease Control and Prevention (CDC) are collaborating to implement this proven intervention in a new 4-year program that will reach 6,000 children at 23 inner-city health care delivery sites throughout the United States. NIAID is extending its work in this area with the Inner-City Asthma Consortium, which was established to explore and evaluate promising new strategies for the treatment of asthma among minority children residing in the inner city. This consortium of basic scientists and clinical investigators conducts clinical studies to elucidate the immunopathogenesis and natural history of asthma in this population.

Vaccination has been recognized as the greatest public health achievement of the 20th century, and vaccine research has long been a cornerstone of the NIAID research portfolio. NIAID-supported research has led to the development of many new and improved vaccines now used widely, such as those against *Haemophilus influenzae* type B, pertussis, chickenpox, pneumococcal disease, and hepatitis A and B. The rapidly evolving science base in pathogen genomics, immunology, and microbiology will facilitate further progress in developing new and improved vaccines. In particular, the availability of the genomic sequences of major microbial pathogens will facilitate the identification of a wide array of new antigens for vaccines. Vaccines that are easy to administer—orally, nasally, or transdermally—will have great utility in resource-poor settings and for mass immunization programs. In addition to the development of vaccines against classic infectious diseases, NIAID is working to develop vaccines against chronic diseases with infectious origins, potential agents of bioterrorism, and autoimmune diseases.

*Profile* describes the Institute's activities in areas of basic research and clinical investigation and provides overviews of the major accomplishments and goals of the various scientific programs within the Institute. *Profile* also includes information on the organization and staff of NIAID, the Institute's budget, and its extramural grants, contracts, and research training programs.

In the 21st century, NIAID is poised to exploit unprecedented scientific opportunities in immunology, microbiology, and infectious diseases. As has been the case for more than 50 years, a commitment to the best possible research—basic science as well as clinical trials—will drive our efforts to improve health in this country and abroad. With a strong research base, the commitment of talented investigators, and the availability of powerful new research tools, we are confident that our initiatives will help solve seemingly intractable public health problems and improve global health in the 21st century.

**Anthony S. Fauci, M.D.**
*Director*
*National Institute of Allergy and Infectious Diseases*

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## Council, Review Committees, and Working Group



## Budget Overview and Historical Trends



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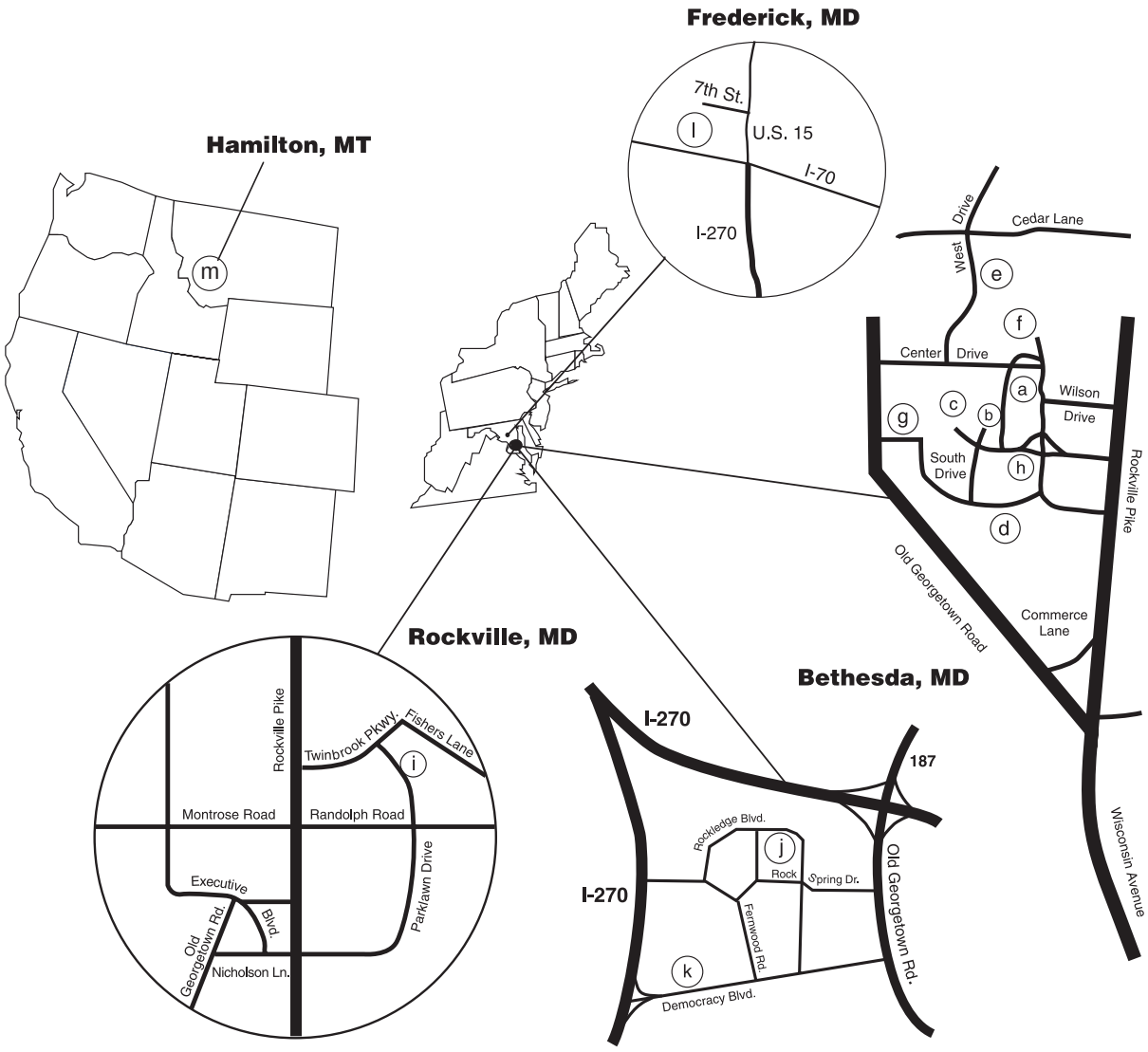
| Linda Coe, R.N., *Associate Clinical Director* | 10 | 11C442 | (301) 402-1420 | lc89m@nih.gov |
| W. Randy Elkins, D.V.M., *Associate Director for Nonhuman Primate Research* | TWNII | 201D | (301) 496-0560 | re9k@nih.gov |
| Wendy J. Fibison, Ph.D., *Associate Director for Special Emphasis Programs* | 7 | 300 | (301) 496-6400 | wf15c@nih.gov |
| Robert Hohman, Ph.D., *Associate Director for Development of Research Technologies* | TWNI | 1004 | (301) 594-8198 | rh13q@nih.gov |
| **Animal Care Branch (ACB)** | | | | |
| W. Randy Elkins, D.V.M., *Acting Chief* | 14BS | 228 | (301) 496-6395 | re9k@nih.gov |
| **Infectious Disease Pathogenesis Branch (IDPB)** | | | | |
| W. Randy Elkins, D.V.M., *Chief* | TWNII | 201D | (301) 496-0560 | re9k@nih.gov |
| **Research Technologies Branch (RTB)** | | | | |
| Robert Hohman, Ph.D., *Acting Chief* | TWNII | 201B | (301) 594-8198 | re9k@nih.gov |
| **Laboratory of Allergic Diseases (LAD)** | | | | |
| Dean D. Metcalfe, M.D., *Chief* | 10 | 11C205 | (301) 496-1267 | dm15o@nih.gov |
| **Laboratory of Cellular and Molecular Immunology (LCMI)** | | | | |
| Ronald H. Schwartz, M.D., Ph.D., *Chief* | 4 | 111 | (301) 496-8108 | rs34r@nih.gov |
| **Laboratory of Clinical Investigation (LCI)** | | | | |
| Stephen E. Straus, M.D., *Chief* | 10 | 11N228 | (301) 496-5807 | ss44z@nih.gov |
| Warren Strober, M.D., *Deputy Chief* | 10 | 11N238 | (301) 496-6810 | ws9j@nih.gov |
| **Laboratory of Host Defenses (LHD)** | | | | |
| John I. Gallin, M.D., *Chief* | 10 | 11N113 | (301) 496-1343 | jg21z@nih.gov |
| Harry L. Malech, M.D., *Deputy Chief* | 10 | 11N113 | (301) 496-1343 | hm5s@nih.gov |
| **Laboratory of Human Bacterial Pathogenesis (LHBP)** | | | | |
| James M. Musser, M.D., *Chief* | RML | | (406) 363-9315 | jm521n@nih.gov |
| **Laboratory of Immunogenetics (LIG)** | | | | |
| Susan K. Pierce, Ph.D., *Chief* | TWNII | 200B | (301) 496-9589 | sp217q@nih.gov |
| **Laboratory of Immunology (LI)** | | | | |
| William E. Paul, M.D., *Chief* | 10 | 11N311 | (301) 496-5046 | wp1k@nih.gov |
| Ronald N. Germain, M.D., Ph.D., *Deputy Chief* | 10 | 11D14 | (301) 496-1904 | rg14b@nih.gov |
| **Laboratory of Immunopathology (LIP)** | | | | |
| Herbert C. Morse III, M.D., *Chief* | 7 | 304 | (301) 496-6379 | hm16c@nih.gov |

| | Bldg. | Room | Phone | E-mail |
|---|---|---|---|---|
| **Laboratory of Immunoregulation (LIR)** | | | | |
| Anthony S. Fauci, M.D., *Chief* | 10 | 11B13 | (301) 496-1124 | af10r@nih.gov |
| **Laboratory of Infectious Diseases (LID)** | | | | |
| Brian R. Murphy, M.D., *Acting Cochief* | 7 | 106 | (301) 496-4205 | bm25f@nih.gov |
| Robert Purcell, M.D., *Acting Cochief* | 7 | 202 | (301) 496-6227 | rp18p@nih.gov |
| **Laboratory of Intracellular Parasites (LICP)** | | | | |
| Harlan D. Caldwell, Ph.D., *Chief* | RML | | (406) 363-9333 | hcaldwell@niaid.nih.gov |
| **Laboratory of Molecular Microbiology (LMM)** | | | | |
| Malcolm A. Martin, M.D., *Chief* | 4 | 315 | (301) 496-4012 | mm54y@nih.gov |
| **Laboratory of Parasitic Diseases (LPD)** | | | | |
| F. Alan Sher, Ph.D., *Acting Cochief* | 4 | 126 | (301) 496-1274 | as28c@nih.gov |
| Thomas E. Wellems, M.D., Ph.D., *Acting Cochief* | 4 | 126 | (301) 496-1274 | tw4i@nih.gov |
| **Laboratory of Persistent Viral Diseases (LPVD)** | | | | |
| Bruce W. Chesebro, M.D., *Chief* | RML | | (406) 363-9354 | bchesebro@nih.gov |
| **Laboratory of Viral Diseases (LVD)** | | | | |
| Bernard Moss, M.D., Ph.D., *Chief* | 4 | 229A | (301) 496-9421 | bm26f@nih.gov |
| **Rocky Mountain Laboratory Microscopy Branch (RMLMB)** | | | | |
| Claude F. Garon, Ph.D., *Chief* | RML | | (406) 363-9228 | cg1t@nih.gov |
| **Rocky Mountain Veterinary Branch (RMVB)** | | | | |
| Michael J. Parnell, D.V.M., Ph.D., *Chief* | RML | | (406) 363-9238 | mp24s@nih.gov |

# Location of Buildings Occupied by NIAID Personnel




**a Building 4**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**b Building 7**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**c Building 10**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**d Building 14B-S**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**e Building 15B-1**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**f Building 31**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**g Building 40/VRC**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**h Building 50**
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

**i Twinbrook II**
12441 Parklawn Drive
Rockville, MD 20852

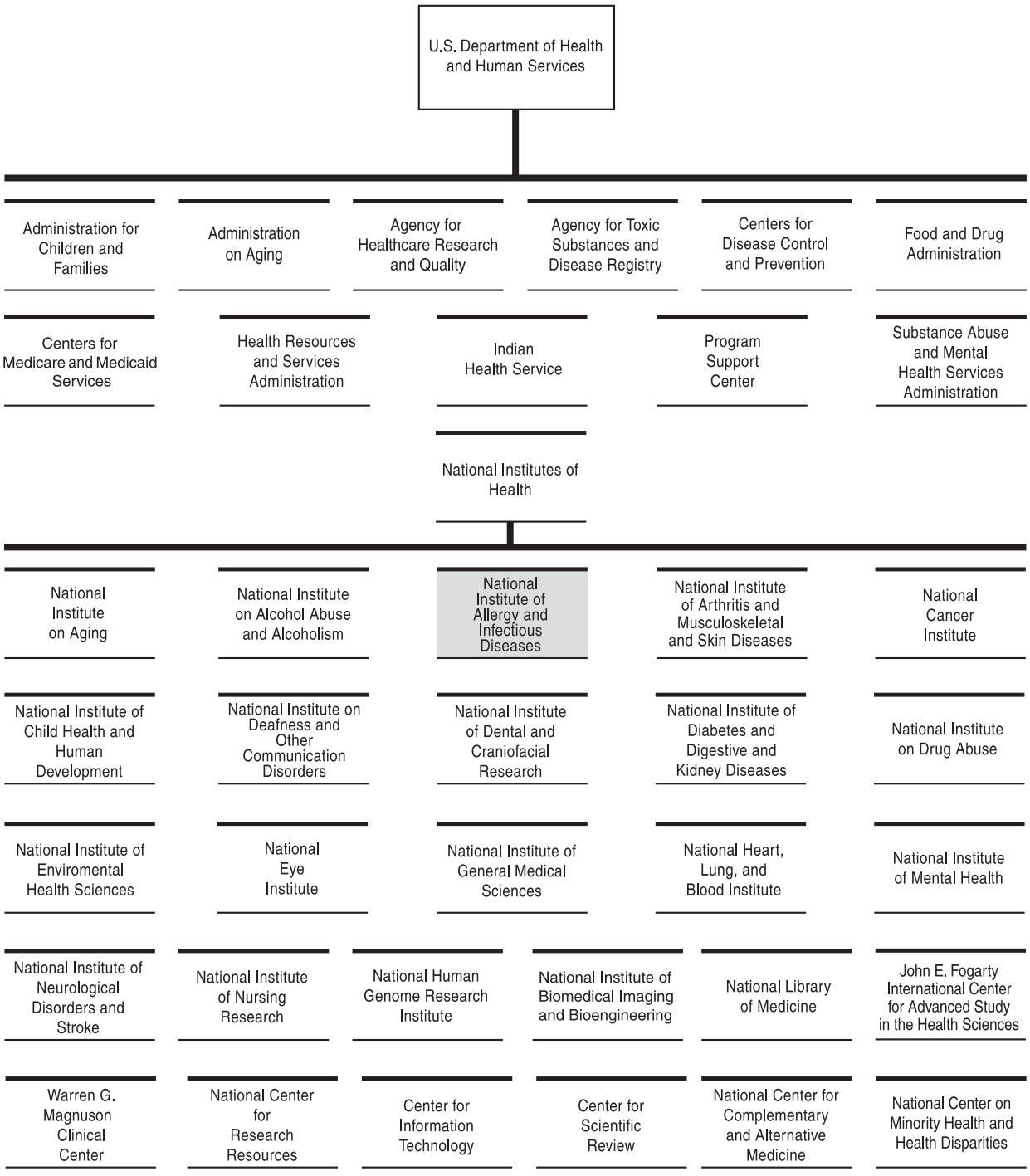
**j Rockledge Building (6700 B)**
6700 B Rockledge Drive
Bethesda, MD 20892

**k Democracy 2**
6707 Democracy Boulevard
Suite 880
Bethesda, MD 20892

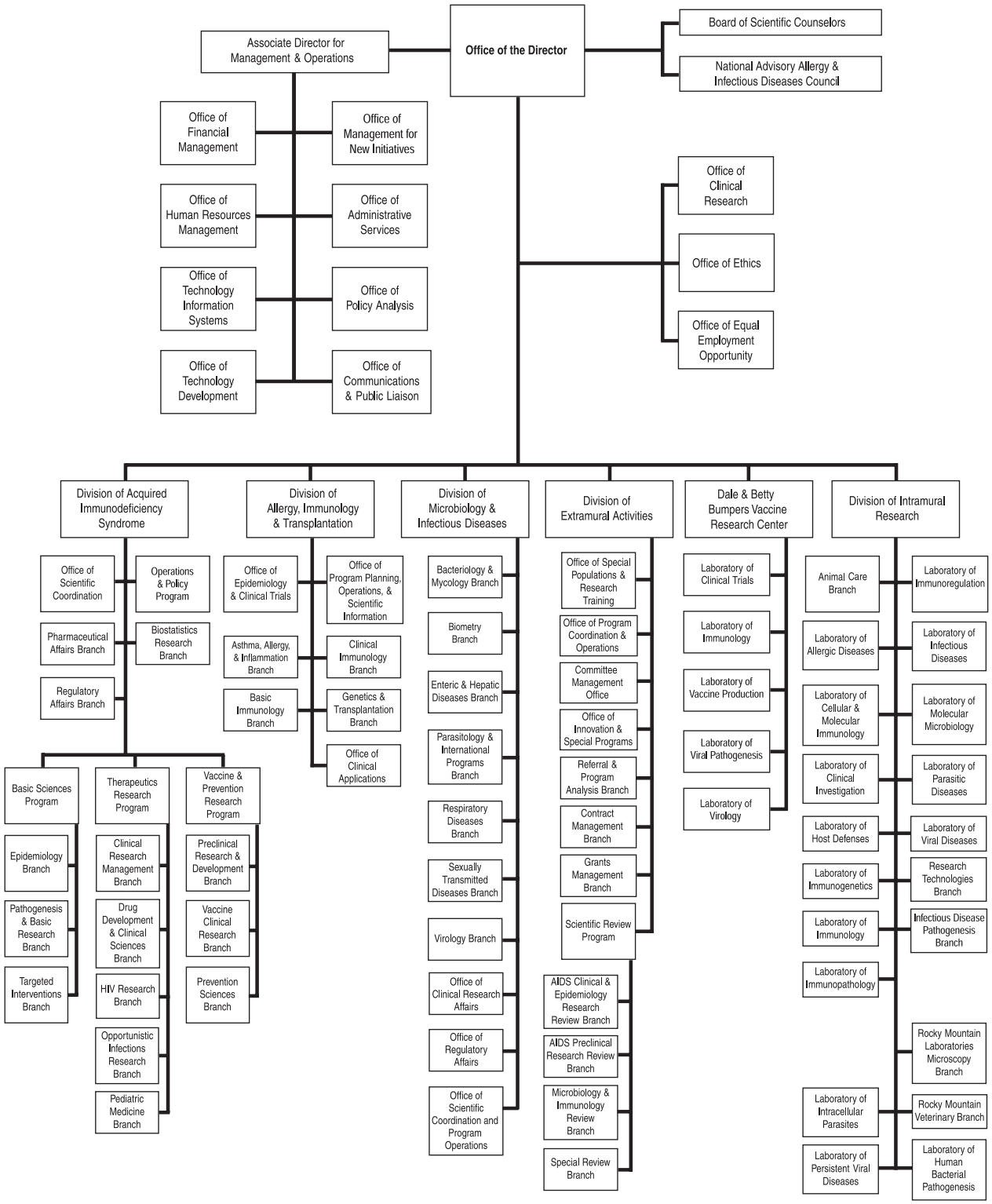
**l Frederick Cancer Research and Development Center**
Building 550
Ft. Detrick, MD 21701

**m Rocky Mountain Laboratories**
903 South Fourth Street
Hamilton, MT 59840

# Location of NIAID in the U.S. Department of Health and Human Services



# NIAID Organizational Chart




Note: The most up-to-date organizational chart is located at www.niaid.nih.gov/organization/default.htm.

## NIAID Director

Anthony S. Fauci, M.D., became the Director of NIAID in 1984. He was born in Brooklyn, New York, and received his undergraduate degree from Holy Cross College in 1962 and his medical degree from Cornell University Medical College in 1966. He completed his internship and residency at The New York Hospital-Cornell Medical Center and joined NIAID in 1968 as a clinical associate in the Laboratory of Clinical Investigation. In 1980, Dr. Fauci became Chief of the NIAID Laboratory of Immunoregulation, a post he continues to hold.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He is an internationally renowned scientist and has pioneered in the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. In addition, Dr. Fauci is recognized widely for delineating the precise mechanisms whereby immunosuppressive agents modulate the human immune response. He has developed effective therapies for formerly fatal diseases such as polyarteritis nodosa, Wegener's granulomatosis, and lymphomatoid granulomatosis.

Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses leading to its susceptibility to deadly infections. He also has delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease as well as for a vaccine to prevent HIV infection. He continues to devote much of his research time to identifying the nature of the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to the AIDS retrovirus.

During his career as a biomedical researcher, Dr. Fauci has authored, coauthored, or edited more than 1,000 scientific publications. He has served as a visiting professor at medical centers throughout the country and has delivered many major lectures at institutions and conferences all over the world. In June 2001, Dr. Fauci was a member of the U.S. delegation to the United Nations General Assembly Special Session on HIV/AIDS.

Dr. Fauci is a member of the prestigious National Academy of Sciences, the American Philosophical Society, the Royal Danish Academy of Science and Letters, the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences, where he is a Council member. He is a member of many professional organizations, including the American College of Physicians, the Infectious Diseases Society of America, the American Society for Clinical Investigation, the Association of American Physicians, and the American Academy of Allergy, Asthma and Immunology. Dr. Fauci serves on a number of editorial boards and is an editor of *Harrison's Principles of Internal Medicine*. He has received numerous awards for his scientific accomplishments, including 22 honorary doctorate degrees.

# Office of the Director

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the focal point of relationships with the Director of the NIH, as well as with other Government agencies, Congress, professional societies, voluntary health agencies, and other public groups. OD's activities also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs.

Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, the OD offices play a key role in helping the Institute achieve its mission. Brief descriptions of the OD offices follow.

The Office of Administrative Services (OAS) helps NIAID staff members carry out their jobs by providing administrative and acquisition management services. These services include procurement, space management, and travel. OAS also develops internal controls in areas such as property accountability and financial monitoring and coordinates and analyzes organizational changes.

The Office of Communications and Public Liaison (OCPL) enables NIAID to meet an important part of its mission by conveying the results of its research programs to health professionals and the public. Through a variety of activities aimed at the media and public and professional audiences, OCPL provides information about the goals and results of NIAID's research programs. In addition to responding to more than 25,000 requests for information annually, the Office plans educational and media campaigns; develops and disseminates brochures, factsheets, press releases, and audiovisual products; and produces educational exhibits for national and regional meetings. OCPL coordinates all activities related to NIAID's homepage on the Internet.

The Office of Financial Management provides overall financial management and budget analysis to the Director and the Institute, as well as budget-related briefing materials for the Director's briefings with the Department of Health and Human Services, Office of Management and Budget, and Congress.

The Office of Human Resources Management provides central human resource services for the executive staff, Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, and employee development.

The newly formed Office of Management for New Initiatives is responsible for managing the establishment of key resources for new scientific and administrative initiatives in NIAID. It also is charged with acquiring and developing physical, human, and contractual infrastructure to fulfill new and expanded NIAID mission requirements.

The Office of Policy Analysis provides overall planning and policy guidance as well as outreach and support. This Office is responsible for Government Performance Results Act and Freedom of Information Act reporting. During FY 2001, the Office

coordinated a revision to NIAID's strategic plan, incorporating the Institute's crosscutting elements on health disparities that reflect the *NIAID Strategic Plan for Addressing Health Disparities.*

The Office of Technology Development administers the Institute's technology transfer activities regarding Cooperative Research and Development Agreements, Material Transfer Agreements, Clinical Trial Agreements, patents, royalties, and related matters.

The Office of Technology Information Systems (OTIS) manages local and wide area network support for NIAID. Moreover, the Office develops applications software and provides application support for NIAID computer databases. The Office also provides training, professional development, and consultative services. In addition, OTIS provides information technology to support NIAID's mission of sponsoring and conducting medical research, and supplies NIAID's intramural and extramural scientific communities and administrative staffs with the capability to readily access, process, and disseminate scientific and administrative information to Congress, the Administration, Federal agencies, other nations, and the public.

The Office of Clinical Research manages and coordinates those NIAID research programs that use the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board, which provides initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office provides any relevant information from NIAID's clinical research programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and people with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities that implement NIH minority-assistance programs and objectives that also relate to the mission of NIAID.

The Office of Ethics provides advice to OD regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee members, and non-Government employees such as peer reviewers or Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

## Outreach Activities

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for dissemination of research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Internet materials; exhibiting materials at professional and community meetings; sponsoring workshops and conferences for community health care providers and the public; and supporting demonstration and education research projects.

OCPL produces materials on topics ranging from allergic and immunologic diseases to AIDS and other sexually transmitted diseases. These materials include press releases, factsheets, and booklets, which are distributed to more than 25,000 people who contact the Institute from around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID web site (www.niaid.nih.gov), which is now visited 800,000 times each month.

The NIAID web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. For example, the Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

A new OCPL communications initiative expands NIAID's efforts to keep more than 200 voluntary and scientific organizations updated about the Institute. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of the organizations. In addition, news from the NIH Offices of Public Liaison, which include NIAID, is also disseminated.

During FY 2001, OCPL wrote and published a pamphlet titled *Microbes in Sickness and in Health*. Microbes, which are minute living organisms such as bacteria, viruses, fungi, and parasites, can be helpful or harmful to the human body. As an informational aid, the pamphlet provides a basic overview of microbes, describes them, and presents information about their history, transmission, treatment, and prevention. The pamphlet will help members of the press write health columns for the lay public, teachers prepare health and biology curricula, and health care workers counsel patients.

OCPL has been involved extensively in the outreach efforts of NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC). The VRC is the first facility at the NIH dedicated solely to vaccine research and production. As the Center begins its first HIV vaccine clinical trial, OCPL is involved in helping to construct local community partnerships by targeting local news media, visiting local churches and other community organizations, and attending HIV/AIDS-related conferences and meetings.

Exhibiting at scientific and health-related meetings is a key element of OCPL's outreach efforts. Institute staff members distribute materials and answer questions about NIAID research and opportunities at conferences, including the American Academy of Allergy, Asthma and Immunology; the National HIV/AIDS Update Conference; the National Medical Association; the American Society for Microbiology; the National Conference on Blacks in Higher Education; the Hispanic Association of Colleges and Universities; and the U.S. Conference on HIV/AIDS.

# Research Planning

NIAID engages in two types of planning: (1) the development and prioritization of specific research initiatives and (2) strategic, long-range planning.

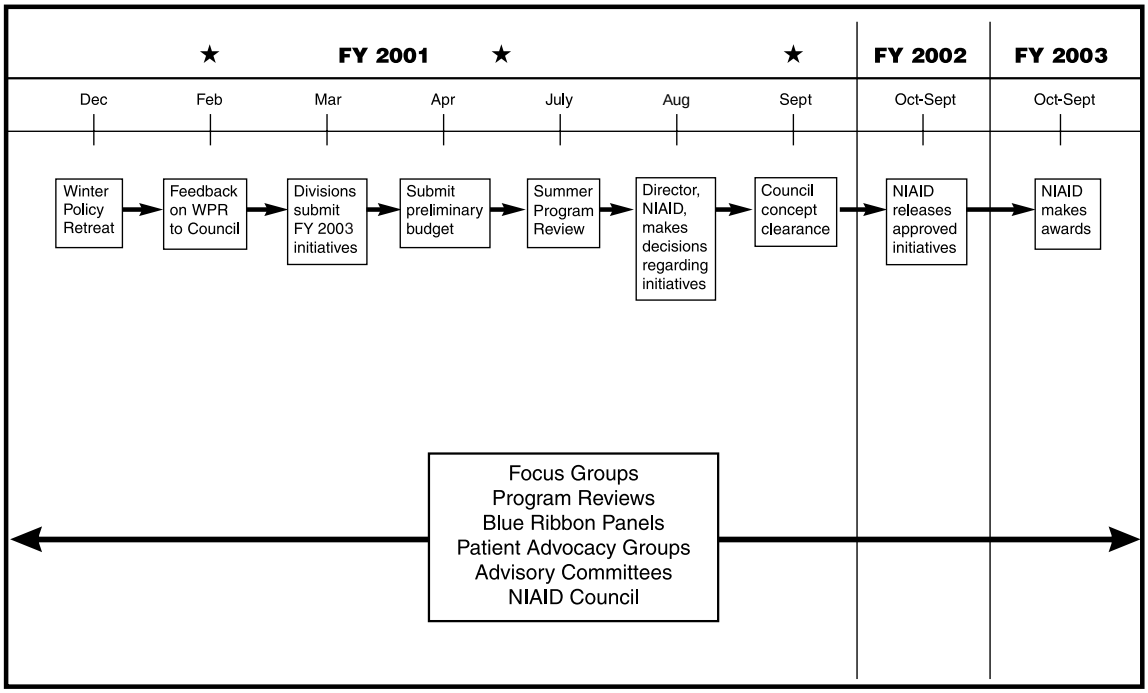
## Planning for Initiatives

NIAID's annual planning process involves developing and selecting initiatives that solicit research applications in specific areas. The process includes a progression of decisionmaking events informed by a continuous stream of reviews, evaluations, and consultations. The two pillars of this process are the Summer Program Review (SPR) and the Winter Policy Retreat (WPR).

The objectives of the SPR include the following:

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify the basis for the opportunities or gaps;
- Identify the relationship between the opportunities or gaps and the needs, special initiatives, or priorities of the Congress, Administration, Department, or NIH Director;
- Propose approaches for responding to the newly identified opportunities or needs;
- Identify implications of changes in scientific or programmatic direction; and

## NIAID Priority-Setting Process




★ - Council meetings

- Prioritize newly identified opportunities or needs within the future budget year.

The planning process is further enriched during the WPR, where the objectives include the following:

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;

- Discuss the scientific framework for and priority of new and renewable programs in the context of the above factors; and

- Use this information to make decisions about activities to be initiated in the future budget year.

NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report titled *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health.*

Throughout the year, NIAID holds scientific workshops, blue ribbon panels, and program reviews to evaluate progress in the field and to determine future needs and opportunities. The NIAID Director and each division consult extensively with NIAID stakeholders; these consultations inform the development of initiatives addressed during the structured planning process. Areas of emphasis articulated in strategic plans and identified by the U.S. Department of Health and Human Services, the NIH, Congress, the White House, and others also help shape the Institute's decisions on whether to alter course or to initiate new activities.

Planning for initiatives begins 2 years in advance of the award year and is a multistep process. At each step in the process, the idea is reviewed and refined. First, a concept for an initiative is subjected to internal review during a retreat. Reviewed and prioritized concepts then are appraised and cleared by the National Advisory Allergy and Infectious Diseases Council (NAAIDC). The divisions then build on the cleared concepts by providing the detailed information required for program announcements, requests for applications, or requests for proposals. The proposed initiatives are released to the scientific community, and applications for funding are accepted. Next, review committees score the applications. Finally, awards are made to those applicants with the highest scores, taking into account programmatic relevance and need.

## Strategic Planning

NIAID's comprehensive strategic plan, *NIAID: Planning for the 21st Century,* is the product of an intensive effort that included a task force of national experts. The document describes broad-based Institute priorities that will guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The cornerstones of the plan are (1) immune-mediated diseases, (2) acquired immunodeficiency syndrome, (3) emerging infectious diseases and global health, and (4) vaccines. The full text of the plan, including descriptions of the opportunities and plans in each of the cornerstone areas, can be accessed at www.niaid.nih.gov/strategicplan.

Another important recent effort in strategic planning focused on how to further stimulate research activities that address the needs of minority and low-income populations. The *NIAID Strategic Plan for Addressing Health Disparities* articulates specific action plans for

reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases, (2) support for infrastructure and research training, and (3) support for outreach. The full text of the health disparities strategic plan can be accessed at www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.

In FY 2001, the Institute also published the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis.* The plan states guiding principles for NIAID global health research and short-, mid-, and long-term research goals. The plan can be accessed at www.niaid.nih.gov/publications/globalhealth/global.pdf.


Currently, NIAID is engaged in an important strategic planning activity regarding research to address the threat of bioterrorism. A draft strategic plan that includes six goal areas (biology of the microbe, host immune response, vaccines, therapeutics, diagnostics, and research resources) was endorsed by a blue ribbon panel in February 2002. The summary of that meeting will be presented to the NAAIDC in June 2002.

# Technology Transfer

Technology transfer in Federal laboratories facilitates the dissemination of new technologies and research materials developed by Government scientists. This technology transfer fuels further innovation and commercialization by the extramural research and development community, ultimately resulting in an improvement in the public health and an increase in the competitiveness of U.S. industry. Federal legislation mandates and defines the Government's technology transfer activities. The key pieces of legislation are the Federal Technology Transfer Act of 1986 and the National Technology Transfer and Advancement Act of 1995.

The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and the development of collaborative relationships between NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Cooperative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADAs), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements (DSAs), and through the NIH Office of Technology Transfer (OTT), the patenting of inventions and the negotiation of various license agreements.

NIAID scientists report inventions to OTD by submitting Employee Invention Reports (EIRs). These EIRs are reviewed by OTD and, with the assistance of the NIAID Technology Evaluation Advisory Committee (TEAC), are evaluated for the purpose of filing domestic and foreign patent applications. In FY 2001, TEAC reviewed 19 intramural EIRs and recommended that a patent application be filed on 16 of them. NIAID currently has 319 active U.S. patent properties, including 125 issued patents and 194 pending patent applications.

NIAID had a total of 190 active license agreements in FY 2000 for both patented inventions and biological materials. These licenses generated about $8.3 million in royalty income, which was first used to pay NIAID inventors their share according to Federal law and NIH policy. The Institute also distributed royalty income to intramural laboratories to support research projects and equipment acquisition that otherwise would not have been accomplished with appropriated funds. The remaining royalties were used to pay OTD's entire operating budget, including patent prosecution fees, OTD staff salaries, associated office expenses, and overhead charged by OTT.

In FY 2001, a total of 119 MTAs, 10 CTAs, 54 CDAs, 7 CRADAs, and 22 M-CRADAs were executed, which OTD negotiated. NIAID scientists performed research under 34 CRADAs and 59 M-CRADAs in FY 2001. The following table provides a history of NIAID's patent, license, and CRADA activities.

**NIAID Technology Transfer Activities**

| Fiscal Year | Pending Patents | Issued Patents | Licenses in Effect | Active CRADAs |
|---|---|---|---|---|
| 1992 | 77 | 48 | 65 | 21 |
| 1994 | 85 | 65 | 84 | 29 |
| 1995 | 96 | 71 | 101 | 31 |
| 1996 | 95 | 84 | 120 | 42 |
| 1997 | 128 | 91 | 131 | 71 |
| 1998 | 154 | 83 | 155 | 95 |
| 1999 | 169 | 94 | 195 | 74 |
| 2000 | 229 | 100 | 196 | 86 |
| 2001 | 194 | 125 | 190 | 93 |

## Technology Transfer Highlights

In FY 2001, OTD negotiated or facilitated the following public-private partnerships.

### *AIDS Vaccine*

Merck and the Dale and Betty Bumpers Vaccine Research Center will collaborate to construct and evaluate adenoviral vectors that encode modified HIV-1 envelope genes for potential use as a component of an HIV-1 vaccine.

### *Rabies Vaccine*

The Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, NIAID, entered into a CRADA with Ligocyte Pharmaceuticals, Inc., for the development and preclinical testing of a rabies DNA vaccine targeted to mucosal tissues in the mouth and nose. The World Health Organization estimates that rabies causes 40,000 to 100,000 human deaths each year, and that 10 to 12 million people in developing countries annually receive one or more doses of injected rabies vaccine after exposure to the virus. This vaccine candidate couples the benefits of DNA vaccines (i.e., ease of construction, ability to induce a full-spectrum of lifelong humoral and cellular immune responses, high temperature stability, and low cost of mass production) with a noninvasive vaccination process that is ideal for developing countries that are poorly equipped for large-scale mass immunization programs, have inadequate health support systems, and must deal constantly with endemic rabies in dog or wild animal populations.

### *Malaria Vaccine*

NIAID and Novavax, Inc., are working together under a CRADA to make and evaluate a candidate malaria vaccine. Current efforts focus on expressing a protein secreted by insect cells that is based on an antigen present in blood-stage parasites of *Plasmodium falciparum,* the malaria parasite responsible for the greatest mortality worldwide. The recombinant protein, called MSP1-42, will subsequently be purified and characterized biochemically and immunologically. Preclinical studies will assess the immunogenicity, optimize the formulation, and provide a preliminary indication of protective efficacy in an animal model. Based on these results, a clinical grade vaccine will be produced for safety and immunogenicity testing in human volunteers. It is hoped that these novel collaborative studies will accelerate the production of a candidate vaccine for a major infectious disease.

### *Murine Lymphocyte Genes*

NIAID and Genetics Institute, Inc., are collaborating under a CRADA to study genes uniquely and exclusively expressed in certain murine lymphocyte populations to understand the molecular mechanisms by which these lymphocytes exert their immunosuppressive effects.

### *NIAID Exchange Program*

NIAID developed an exchange program—managed by Taconic Farms, Inc., a U.S. Government contractor—to raise, breed, and distribute valuable immunologic mouse models to researchers outside of the NIH. Extramural

NIAID funds partially underwrite the costs of this program to provide ready access to emerging mouse models. In FY 2001, NIAID began expanding the program and added three mouse models to the five strains currently available.

## New CRADAs

During FY 2001, NIAID scientists entered into the following eight new CRADAs:

- **Achillion Pharmaceuticals**—John Inman, Ph.D., and Ettore Appella, M.D., "Development of Optimized Inhibitors of Protein Zinc Finger Domains"

- **Genetics Institute**—Ethan Shevach, M.D., "Analysis of Gene Expression in Immunoregulatory T Cells That Co-express the CD4 and CD25 Surface Markers"

- **Glaxo Research and Development**—Clifton Barry, Ph.D., "Development of New Drugs for the Treatment of Tuberculosis"

- **LigoCyte Pharmaceuticals**—Donald Lodmell, Ph.D., "Mucosal Vaccination of Mice Using an M Cell Targeted Adhesion Protein-Rabies DNA Vaccine Construct"

- **Merck—**Gary Nabel, M.D., Ph.D., "Development of an Adenoviral-Based HIV Vaccine"

- **Nexell Therapeutics—**Harry Malech, M.D., and Mitchell Horwitz, M.D., "Study of Low-Intensity Preparative Regimen Followed by HLA-Matched Transplantation for Chronic Disease"

- **Novartis—**Marshall Plaut, M.D., "A Double-Blind, Placebo-Controlled Study of the Efficiency of E25 Anti-IgE in Reducing Asthma Symptoms in Inner-City Children"

- **Novavax—**Louis Miller, M.D., "Merozoite Surface Protein 1 Expressed in Insect Cells: Process Development, Preclinical, and Initial Clinical Evaluation"

## CRADAs in Effect, FY 2001

| Investigator | Company | Title |
|---|---|---|
| Clifton Barry, Ph.D.<br>Laboratory of Host Defenses | Glaxo Research and Development | Development of new drugs for the treatment of tuberculosis |
| Clifton Barry, Ph.D.<br>Laboratory of Host Defenses | Pharmacopeia | Screening *Mycobacterium tuberculosis* |
| Clifton Barry, Ph.D.<br>Laboratory of Host Defenses | Sequella, Inc. | High synthesis and screening |
| Jeffrey Cohen, M.D.<br>Laboratory of Clinical Investigation | Wyeth-Lederle Vaccines | Identification of varicella-zoster gene targets |
| Peter Collins, Ph.D.<br>Laboratory of Infectious Diseases | Lederle-Praxis<br>American Cyanamid | Production of live attenuated respiratory syncytial virus (RSV) and parainfluenza virus (PIV) vaccine viruses from cDNA |
| MaryAnn Guerra<br>Larry Wolfe, Ph.D.<br>Office of Technology and Information Systems | Biospace.com | Development of an electronic procurement system for commodity identification, product and service acquisition, and budget tracking |
| B. Fenton Hall, M.D., Ph.D.<br>Division of Microbiology and Infectious Diseases | Genzyme Transgenics | Transgenic malaria vaccines: process development; preclinical and initial clinical evaluation |
| John Inman, Ph.D.<br>Laboratory of Immunology<br>Ettore Appella, M.D.<br>National Cancer Institute | Achillion Pharmaceuticals | Development of optimized inhibitors of protein zinc finger domains |
| Albert Z. Kapikian, M.D.<br>Laboratory of Infectious Diseases | Wyeth-Lederle Vaccines | Development of a live orally administered rhesus rotavirus vaccine |
| David Kaslow, M.D.<br>Laboratory of Parasitic Diseases | Hong Kong Institute of Biotechnology | An antimalaria transmission-blocking vaccine: process development, scale-up, and manufacturing |
| David L. Klein, Ph.D.<br>Division of Microbiology and Infectious Diseases | GlaxoSmithKline | Adult pertussis vaccine |
| H. Clifford Lane, M.D.<br>Laboratory of Immunoregulation | Cell Genesys | Adoptive transfer of human T-cell clones for treatment of immunologically mediated and infectious diseases |
| H. Clifford Lane, M.D.<br>Laboratory of Immunoregulation | Chiron | Research and development of interleukin-2 as a treatment for HIV infection |

| Investigator | Company | Title |
|---|---|---|
| Catherine Laughlin, Ph.D.<br>Stephen Straus, M.D.<br>Division of Microbiology and Infectious Diseases | Protein Design Labs | Production and clinical evaluation of human anti-herpes simplex virus (HSV) monoclonal antibody as a therapeutic agent for the treatment of neonatal HSV infections |
| Donald Lodmell, Ph.D.<br>Laboratory of Persistent Viral Diseases | LigoCyte Pharmaceuticals | Mucosal vaccination of mice using an M cell targeted adhesion protein-rabies DNA vaccine construct |
| Harry L. Malech, M.D.<br>Laboratory of Host Defenses | Nexell Therapeutics | *Ex vivo* stem cells chronic granulomatous disease |
| Harry L. Malech, M.D.<br>Mitchell Horwitz, M.D.<br>Laboratory of Host Defenses | Nexell Therapeutics | Study of low-intensity preparative regimen followed by HLA-matched transplantation for chronic disease |
| Pamela McInnes, Ph.D.<br>Division of Microbiology and Infectious Diseases | Wyeth-Lederle Vaccines | Preventing childhood mortality—an efficacy trial of a pneumococcal conjugate vaccine in Upper and Central River Divisions, The Gambia |
| Pamela McInnes, Ph.D.<br>Division of Microbiology and Infectious Diseases | Aviron | Development of a live attenuated cold-adapted influenza vaccine |
| Louis Miller, M.D.<br>Laboratory of Parasitic Diseases | Hong Kong Institute of Biotechnology | Process development, scale-up, manufacturing, and initial clinical testing of a recombinant subunit malaria vaccine produced in yeast |
| Louis Miller, M.D.<br>Laboratory of Parasitic Diseases | Novavax | Merozoite surface protein 1 expressed in insect cells: process development, preclinical, and initial clinical evaluation |
| Brian R. Murphy, M.D.<br>Laboratory of Infectious Diseases | Lederle-Praxis<br>American Cyanamid | Development of safe and effective live attenuated vaccines for respiratory syncytial virus subgroups A and B and parainfluenza viruses type 1, 2, and 3 |
| Brian R. Murphy, M.D.<br>Laboratory of Infectious Diseases | Lederle-Praxis<br>American Cyanamid | Development of the cold-adapted PIV3 vaccine virus |
| Marshall Plaut, M.D.<br>Division of Allergy, Immunology and Transplantation | Novartis | A double-blind, placebo-controlled study of the efficiency of E25 anti-IgE in reducing asthma symptoms in inner-city children |
| Calman Prussin, M.D.<br>Laboratory of Allergic Diseases | Immunex | Phase II efficacy study of aerosolized recombinant human interleukin-4 receptor in adults with asthma |

| Investigator | Company | Title |
|---|---|---|
| Robert H. Purcell, M.D.<br>Laboratory of Infectious Diseases | GlaxoSmithKline | Hepatitis C vaccine |
| Robert H. Purcell, M.D.<br>Laboratory of Infectious Diseases | GlaxoSmithKline | Hepatitis E vaccine |
| M. Robert-Guroff, Ph.D.<br>National Cancer Institute<br>Mark Connors, M.D.<br>Laboratory of Immunoregulation | Lederle-Praxis Biologicals | HIV recombinants—development of HIV vaccine |
| Alexander Rosenthal<br>John McGowan, Ph.D.<br>Division of Extramural Activities | RAMS, Inc. | Development of integrated systems |
| Ethan Shevach, M.D.<br>Laboratory of Immunology | Genetics Institute | Analysis of gene expression in immunoregulatory T cells that co-express the CD4 and CD25 surface markers |
| Stephen Straus, M.D.<br>Warren Strober, M.D.<br>Peter Mannon, M.D.<br>Laboratory of Clinical Investigation | Genetics Institute | A randomized, double-blind, placebo-controlled, dose-finding, safety study of two parallel dose levels of subcutaneously administered human monoclonal antibody to interleukin-12 (J695) in patients with active Crohn's disease |
| Stephen Straus, M.D.<br>Laboratory of Clinical Investigation | Merck | A double-blind, placebo-controlled study of the efficacy of live attenuated Oka/Merck varicella-zoster vaccine in reducing the incidence and/or severity of shingles in adults |
| Warren Strober, M.D.<br>Laboratory of Clinical Investigation | Aventis Pasteur | Development of vectored vaccines and therapeutics for the prevention and treatment of AIDS |
| Tom Wynn, Ph.D.<br>Laboratory of Parasitic Diseases | Genetics Institute | Development of interleukin-13 antagonism as a treatment for fibrosis in schistosomiasis |

# Division of Extramural Activities

The Division of Extramural Activities (DEA) (www.niaid.nih.gov/ncn) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's training program, and conducting initial peer review for funding mechanisms with Institute-specific needs. DEA also provides broad policy guidance to Institute management and oversight of all of NIAID's chartered committees. The Office of the Director, DEA, is a long-time leader of NIH reinvention experiments, including the creation of innovative electronic systems that have changed NIAID and NIH operations.

DEA staff members in every part of the organization interact intensively with grantees, contractors, reviewers, members of the National Advisory Allergy and Infectious Diseases Council (NAAIDC), and applicants, as well as with the staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome, the Division of Allergy, Immunology and Transplantation, and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch issues all NIAID grant awards after negotiating the terms of the grant award with the applicant. Specialists in the Branch determine the amount of the award, develop the administrative terms and conditions, and release the official award document. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowable and how to formulate a budget for a grant application. Grant specialists supervise day-to-day administrative and financial management of Institute grants and cooperative agreements, while ensuring that NIAID's grants are in compliance with existing policies. They are sources of valuable information on existing and new policies that may alter a grantee's requirements and privileges and that can inform grantees about which actions need approval and from whom.

Contract specialists manage the administrative aspects of NIAID's research and development contract portfolio. Toward those ends, they help develop requests for proposals, negotiate the technical and business aspects of proposals, and select the offeror. Working in DEA's Contract Management Branch (CMB), contract specialists are well versed in a full range of legal, technical, business, and cost-related topics, including Federal Acquisition Regulations and other policies and procedures. They provide investigators with guidance on changes in the scope of the research, the allowability of costs, and other administrative issues, including the use of contract funds, the technical or administrative performance of a contract, current or anticipated initiatives, and changes to a contract. For more information about contracts, go to CMB's web site at www.niaid.nih.gov/contract.

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications and requests for proposals. Working in DEA's SRP, Institute review staff members assist investigators and NIAID staff members with issues related to grant and proposal preparation, including application format and documentation requirements. They also can provide insights into the peer review process

and plans for specific review meetings; give advice on applying for a grant, including special review criteria and other requirements of NIAID program announcements, requests for applications, and requests for proposals; answer questions about the assignment or scheduling of applications or proposals for review; and advise applicants on NIH policy requirements. SRP manages NIAID's three chartered review committees and convenes special emphasis panels as needed.

DEA's Referral and Program Analysis Branch (RPAB) is the Institute's referral point for grant applications. RPAB also performs scientific classification and data analysis of all funded grants, contracts, and intramural research projects, including the categorization and analysis needed to generate official NIAID science-information reports.

Several offices and staff members in DEA's Office of the Director play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including small business programs (Small Business Innovation Research [SBIR] and Small Business Technology Transfer [STTR]), Academic Research Enhancement Award (AREA) grants, Council activities, and extramural communications. They develop policies and processes for NIAID's extramural research programs, including innovative electronic systems, and provide guidance on grant requirements and procedures to investigators.

The Office of Special Populations and Research Training (OSPRT) oversees NIAID's portfolio of training grants, fellowships, and career development awards. Staff members in this Office answer questions that applicants have about training-type support awards supported by NIAID. In addition, OSPRT administers the Research Supplements for the Underrepresented Minorities Program, which supports young minority scientists on NIAID-funded research grants.

The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, special emphasis panels, and three review committees.

To keep the Institute's extramural research community informed and to provide advice on many research and policy topics, DEA produces the NIAID *Council News* newsletter and sponsors the *Council News* Extramural Information Center on the World Wide Web (www.niaid.nih.gov/ncn). These outreach resources keep grantees, applicants, and staff members up to date on Institute funding opportunities, policy changes, and other news. They also educate our extramural constituency by providing budget and payline information, a glossary of NIH terms and acronyms, articles on complex subjects such as percentiling, and advice on writing a grant application.

# Division of Acquired Immunodeficiency Syndrome

## Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) (www.niaid.nih.gov/daids) was formed in 1986 to develop and implement the national research agenda to address the HIV/AIDS epidemic. Today, with the ever-changing demographics of the epidemic, DAIDS is expanding its focus to a more global research agenda with an emphasis on an integrated prevention and therapeutics agenda in developing nations. Specifically, the mission of DAIDS is to help ensure an end to the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus, or HIV, supporting the development of therapies for HIV infection and its complications, and supporting the development of vaccines and other prevention strategies. DAIDS accomplishes its mission through planning, implementing, managing, and evaluating programs in (1) fundamental basic research, (2) discovery and development of therapies and treatment strategies for HIV infection and its complications, and (3) discovery and development of vaccines, topical microbicides, and other prevention strategies. To achieve its mission, DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. By surveying developments in key research areas, DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with advisory groups and community and health professional organizations, evaluating and redirecting program emphasis to respond to changing global research needs.

## Scientific Areas of Focus

### *Basic Research*

Basic research continues to increase our understanding of the biology of HIV and how the immune system responds to the virus. Knowledge gained from these studies enhances the ability of researchers to create new therapeutic agents and vaccines to combat HIV infection. DAIDS supports a large portfolio of investigator-initiated grants in HIV pathogenesis and epidemiology that are pursuing research in a variety of areas, including mechanisms of viral entry and infection; the structure, function, and mechanism of action of viral genes and proteins; the roles of cellular accessory molecules in replication; the immunologic and virologic events controlling primary infection and formation of the latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, in recent years, DAIDS-funded investigators have identified new structures for viral components of HIV, how HIV uses the host machinery to exit the cell, and the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication and about why the host immune response is not fully effective in controlling the infection. Information about

how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

### *Therapeutics*

The Division's therapeutics research program supports the discovery and development of effective therapies for HIV/AIDS and associated opportunistic infections (OIs) by facilitating and expediting research on highly promising candidate agents and novel therapeutic concepts. Through strategic planning and funding, DAIDS supports research on potential new cellular and viral therapeutic targets, enhanced formulations of existing agents, and treatment regimens to improve adherence, minimize toxicities, and impede emergence of resistance. In addition, the Division supports research on approaches to restore the immune system, to protect uninfected cells, and to improve assays to measure pathogen load and host immunity. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans. The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. These clinical studies define new agents that are effective against HIV and its associated OIs and clarify how best to use these drugs. Human testing of anti-HIV therapeutics is carried out in three large DAIDS-sponsored clinical trials networks: the Adult AIDS Clinical Trials Group (AACTG) (http://aactg.s-3.com), the Pediatric AIDS Clinical Trials Group (PACTG) (http://pactg.s-3.com), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) (www.cpcra.org). In addition, research on acute HIV infection is conducted through the Acute HIV Infection and Early Disease Research Program (AIEDRP) (http://aiedrp.fhcrc.org).

DAIDS-sponsored therapeutics research already has had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define national and international guidelines for the treatment of primary HIV infection and associated OIs as well as prophylactic regimens for these secondary infections, (2) identified biological markers, such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression, and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-infant transmission of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and ways to rebuild and replace immunity lost to HIV infection. In addition, the Division is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy and the most optimal approaches to medical management.

### *Vaccine and Prevention Research*

The development of safe and effective vaccine and nonvaccine strategies for the prevention of HIV infection and AIDS is a high priority of NIAID. DAIDS supports all phases of the discovery and development of preventive HIV vaccines, including basic research, preclinical testing, and human clinical testing of candidate HIV vaccines. Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (www.hvtn.org). The HVTN, which was formed in 2000, is a global network designed to develop and conduct a comprehensive HIV vaccine clinical research agenda that addresses the scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. The HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. (Additional information on the HVTN is located in the Vaccine Research and Development section of Selected Scientific Areas of Interest on page 88.)

DAIDS also supports research on other biomedical and behavioral approaches to preventing the spread of HIV/AIDS. These approaches include drugs or vaccines that prevent mother-to-infant HIV transmission, microbicides for preventing sexual transmission of HIV, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted diseases, and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners. NIAID-supported prevention clinical trials are centered in the HIV Prevention Trials Network (HPTN) (www.hptn.org). The HPTN, also formed in 2000, is a global, multicenter network dedicated to prevention research with a focus on HIV end points. The HPTN is supported by the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse. (Additional information on the HPTN is located in the AIDS section of Selected Scientific Areas of Interest on page 56.)

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, further explained the envelope structure of HIV, advanced our understanding of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes (CTLs), developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies must address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. With regard to other prevention research, new microbicides must be developed and tested to prevent the sexual transmission of HIV. In addition, to build on its past success in identifying an inexpensive regimen that

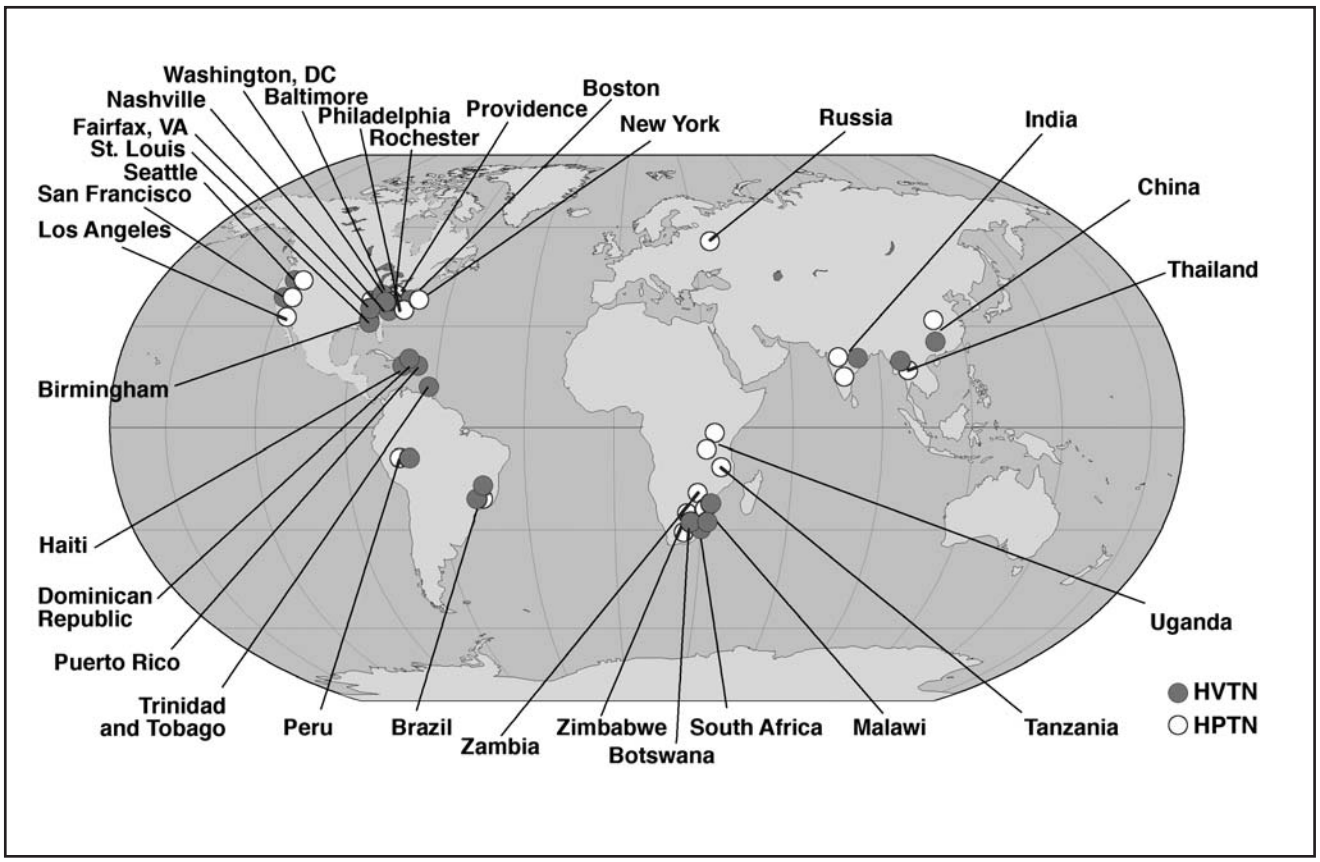
reduces HIV transmission at birth, the Division must develop new, more effective regimens for preventing the maternal-infant transmission of HIV, especially during breastfeeding. These regimens must be practical for use in developing countries.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's vaccine and prevention research activities are conducted on a global scale. These research programs are designed to advance global research priorities, ensure the clinical relevance of future vaccine and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

## Major Programs and Networks

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- Comprehensive International Program of Research on AIDS
- HIV Prevention Trials Network
- HIV Therapeutics: Targeting Research Gaps
- HIV Vaccine Design and Development Teams
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Research and Design Program
- HIV Vaccine Trials Network
- Innovative Grant Program
- Integrated Preclinical/Clinical Program for HIV Topical Microbicides
- Integrated Preclinical/Clinical Vaccine Development Program
- Laboratory Methods to Assess Responses to HIV Vaccine Candidates
- Multicenter AIDS Cohort Study
- National Cooperative Drug Discovery Groups—Opportunistic Infections
- New Technologies for HIV and HIV Vaccine-Related Research
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Therapeutics Research on AIDS and Associated Opportunistic Infections
- Women and Infants Transmission Study
- Women's Interagency HIV Study

# NIAID HIV Vaccine and Prevention Trials Networks (HVTN and HPTN) Domestic and International Sites




The HVTN domestic and international clinical sites and their principal investigators are listed below.

## United States

### Alabama

- University of Alabama at Birmingham—Mark Mulligan, M.D.

### California

- San Francisco Department of Health, San Francisco—Susan Buchbinder, M.D.
- Mount Zion Hospital, San Francisco—Susan Buchbinder, M.D.

### Maryland

- University of Maryland, Baltimore—William Blattner, M.D.
- Johns Hopkins University, Baltimore—Donald Burke, M.D.

### Massachusetts

- Fenway Community Health, Boston—Kenneth Mayer, M.D.
- Harvard University—Brigham and Women's Hospital, Boston—Raphael Dolin, M.D., and Lindsay Baden, M.D.

**Missouri**

- Saint Louis University—Robert Belshe, M.D.

**New York**

- Columbia University, New York—Scott Hammer, M.D.
- New York Blood Center—Union Square, New York—Beryl Koblin, Ph.D.
- New York Blood Center—Bronx, New York—Beryl Koblin, Ph.D.
- University of Rochester, Rochester—Michael Keefer, M.D.

**Puerto Rico**

- Universidad de Puerto Rico, San Juan—Carmen Zorrilla, M.D.

**Rhode Island**

- Miriam Hospital, Providence—Kenneth Mayer, M.D.

**Tennessee**

- Vanderbilt University, Nashville—Peter Wright, M.D.

**Virginia**

- University of Maryland, Fairfax—William Blattner, M.D.

**Washington**

- Fred Hutchinson Cancer Research Center and University of Washington, Seattle—Julie McElrath, M.D.

**Washington, D.C.**

- Johns Hopkins University Center for Immunization Research, Washington, D.C.—Donald Burke, M.D.

## International

**Africa**

*Botswana*

- Botswana-Harvard Partnership for HIV Research and Education—Princess Marina Hospital, Gaborone—Myron Essex, D.V.M., Ph.D.

*South Africa*

- South African Medical Research Council, Durban—Glenda Gray, M.D.
- Chris Hani Baragwanath Hospital, Soweto—Glenda Gray, M.D.

**Asia**

*China*

- Guangxi Health and Anti-Epidemic Center, Guangxi—Jie Chen, M.D.

*India*

- National AIDS Research Institute, Pune—Ramesh Paranjape, M.D.

*Thailand*

- Research Institute for Health Sciences, Chiang Mai—Thira Sirisanthana, M.D.

### South America and the Caribbean

*Brazil*

- Hospital Escola Sao Francisco de Assis, Rio de Janeiro—Mauro Schechter, M.D., Ph.D.

*Dominican Republic*

- Centro Orientacion Integral/Instituto Dermatologica, Santo Domingo—Luis Moreno, M.D., and Claudio Volquez, M.D.

*Haiti*

- GHESKIO, Port-au-Prince—Jean William Pape, M.D.

*Peru*

- Associacion Civil Impacta Salud y Educacion, Lima—Jorge Sanchez, M.D., M.P.H.

*Trinidad and Tobago*

- Medical Research Foundation of Trinidad and Tobago, Port of Spain—Courtenay Bartholomew, M.D., FRCP

The HPTN domestic and international clinical sites and their principal investigators are listed below.

## United States

### Alabama

- University of Alabama at Birmingham—Sten Vermund, M.D., Ph.D.

### California

- Los Angeles County Department of Health—Peter Kerndt, M.D., M.P.H.
- University of California at Los Angeles—Yvonne J. Bryson, M.D.
- University of California at San Francisco—Tsungai Chipato, MBChB

### Maryland

- Johns Hopkins University, Baltimore—Robert C. Bollinger, M.D., M.P.H.
- Johns Hopkins University, Baltimore—David Celentano, Sc.D., M.P.H.
- Johns Hopkins University, Baltimore—Laura Guay, M.D.
- Johns Hopkins University, Baltimore—J. Brooks Jackson, M.D., M.B.A.
- Johns Hopkins University, Baltimore—Taha E. Taha, M.D., Ph.D.

### Massachusetts

- Fenway Community Health, Boston—Kenneth H. Mayer, M.D.
- Harvard University School of Public Health, Boston—Wafaie Fawzi, M.D., Dr.P.H.

### New York

- Columbia University Health Sciences, New York—Wafaa El-Sadr, M.D., M.P.H.

### North Carolina

- University of North Carolina, Chapel Hill—Robert Ryder, M.D.

### Pennsylvania

- University of Pennsylvania, Philadelphia—David Metzger, Ph.D.

### Washington

- Harborview Medical Center, Seattle—Connie Celum, M.D., M.P.H.

## International

### Africa

*Malawi*

- Malawi College of Medicine, Blantyre—George Liomba, M.D.

*South Africa*

- South African Medical Research Council, Durban—Gita Ramjee, M.D.

*Tanzania*

- Muhimbili University, College of Health Sciences, Dar Es Salaam—Gernard Msamanga, M.D., D.Sc.

*Uganda*

- Makerere University School of Medicine, Kampala—Francis Mmiro, MBChB
- Makerere University School of Medicine, Kampala—Nelson Sewankambo, M.D.

*Zambia*

- Lusaka District Health Board and University Teaching Hospital, Lusaka—Moses Sinkala, M.D., and Chewe Lou, M.D., M.Sc.

*Zimbabwe*

- University of Zimbabwe, Harare—Tsungai Chipato, MBChB

### Asia

*China*

- National Center for AIDS Prevention and Control, Beijing—Yiming Shao, M.D., Ph.D.

*India*

- IHI/YRG Care, Chennai—Suniti Solomon, M.D.
- National AIDS Research Institute, Pune—Sanjay M. Mehendale, M.D., MBBS, M.P.H.

*Thailand*

- Chiang Mai University, Chiang Mai—Chirasak Khamboonruang, M.D., Ph.D.

### Europe

*Russia*

- St. Petersburg State University—Andrei Kozlov, Ph.D.

### South America

*Brazil*

- Oswaldo Cruz Foundation, Rio de Janiero—Francisco Inacio Bastos, M.D.

*Peru*

- Universidad Peruana Cayetano Heredia, Lima—Jorge Sanchez, M.D., M.P.H.

# Division of Allergy, Immunology and Transplantation

The immune system is a complex network of specialized cells and organs. When it malfunctions, it can cause a wide array of problems. Scientists are making great strides in detecting, treating, and preventing disorders of the immune system. The Division of Allergy, Immunology and Transplantation (DAIT) (www.niaid.nih.gov/research/dait.htm) supports research that focuses on understanding the important role of the immune system in the pathogenesis, treatment, and prevention of many immune-mediated disorders, including asthma and allergic diseases; autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus; inherited primary immunodeficiency diseases; and the immune-mediated graft rejection in solid organ, tissue, and cell transplantation. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes of immune-mediated diseases and to apply this knowledge to the development of improved approaches to disease diagnosis, treatment, and prevention through demonstration and education research projects. DAIT evaluates the effectiveness of behavioral and educational interventions to promote health and prevent disease in defined populations.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further our understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including basic biology of the immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on a broad spectrum of diseases, including those that affect the intestines, joints, nervous system, and endocrine system. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune disease, and methods of immune intervention. In addition, support is provided

for research on the causes and underlying immune mechanisms of various inherited immunodeficiency diseases, such as severe combined immunodeficiency disease.

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment. Through the Inner-City Asthma Study, DAIT supports a multicenter clinical intervention to reduce asthma severity among inner-city children.

Immune tolerance is a high priority for NIAID, and as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN) in FY 1999. The ITN, cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, conducts clinical trials of promising tolerogenic approaches, carries out integrated studies of underlying mechanisms, and develops biomarkers and assays to measure the induction, maintenance, and loss of tolerance in humans. This international, multi-institutional research program is focused on four clinical areas: kidney transplantation, islet transplantation, autoimmune diseases, and asthma and allergic diseases.

Autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis, are estimated to afflict 5 to 8 percent of the U.S. population and are a major cause of chronic disability, particularly among women. DAIT-supported programs in this area promote the integration of basic and clinical research as well as interdisciplinary and trans-NIH collaborations to elucidate mechanisms of the pathogenesis of autoimmunity and autoimmune diseases, including basic molecular and cellular studies, genetic studies, development of new therapeutics, and preclinical and clinical research.

The Division's basic research in transplantation immunology and genetics seeks to define the organization and effects of gene expression on immune function and to determine the manner in which the products of gene expression control the immune response to foreign substances, such as transplanted organs and cells. In addition, DAIT supports individual research projects focused on the regulation of the immune response and program projects in transplantation immunology. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trials in Adult Kidney Transplantation and the Cooperative Clinical Trials in Pediatric Kidney Transplantation.

## Primary Research Areas

### *Asthma and Allergic Diseases*

- Asthma and Allergic Diseases Research Center
- Inner-City Asthma Study

### *Autoimmune Diseases*

- Autoimmunity Centers of Excellence
- Cooperative Study Group for Autoimmune Disease Prevention
- Clinical Trials in Stem Cell Transplantation for the Treatment of Autoimmune Diseases
- Clinical Trials and Clinical Markers in Immune-Mediated Diseases
- Diabetes Centers of Excellence

### *Basic and Clinical Immunology*

- Human Immunology Centers of Excellence
- Hyperaccelerated Award/Mechanisms in Immune Disease Trials
- Vaccine Immunology Basic Research Centers

### *Immune Tolerance*

- Immune Tolerance Network
- Non-human Primate Transplantation Tolerance Cooperative Study Group
- Innovative Grants in Immune Tolerance
- Innovative Research in Human Mucosal Immunity

### *Transplantation*

- Cooperative Clinical Trials in Adult Kidney Transplantation
- Cooperative Clinical Trials in Pediatric Kidney Transplantation
- Immunopathogenesis of Chronic Graft Rejection

# Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to diagnose, treat, and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports projects spanning the entire spectrum of biomedical research from early basic research through phase III clinical trials.

DMID-supported basic research includes studies on molecular structure and function, host/pathogen interactions, genetics, and physiologic and biochemical processes of bacteria, viruses, fungi, and parasites. These studies provide basic insights that help in identifying new antigens for vaccines and drug targets. Knowledge gained from basic research also helps in understanding how pathogens emerge and cause infection and disease.

The Division also supports more focused, applied research. These programs include development, preclinical testing, and clinical trials of new vaccines, antivirals, antifungals, and antimicrobials. DMID also funds projects to sequence the full genomes of a number of medically important microbes. Pathogen genomes can be used to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

## Scientific Areas of Focus

### *Vaccine Development*

One of the primary goals of the Division is to develop new and improved vaccines for preventing infectious diseases. Recombinant DNA technology, the production of monoclonal antibodies by hybridomas, nucleic acid sequencing, and peptide synthesis are providing researchers with new ways of producing more highly specific immunogenic antigens that can be incorporated into vaccines. These advances, coupled with the possibilities for manipulation of antibody and cellular immune responses, offer hope for preventing and ultimately eradicating many diseases that are not covered by current vaccines. These advances also enhance the possibility of improving the currently available vaccines.

Since 1981, DMID has supported a program for the accelerated development of new vaccines to take advantage of advances in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program has contributed to the development of new vaccines for *Haemophilus influenzae* type B, pneumococcal pneumonia, and pertussis (whooping cough). Among a longer list of research priorities for production of new and improved vaccines are those that protect against viral hepatitis, enteric pathogens (including rotaviruses and cholera), sexually transmitted diseases (STDs), parasitic diseases, tuberculosis (TB), and systemic fungal infections. The Division's *Jordan Report*, which provides an overview of the state of the science for vaccine research, can be viewed online at www.niaid.nih.gov/publications/pdf/jordan.pdf.

DMID also supports research to develop novel vaccine delivery methods, such as transgenic plant vaccines (potatoes and tomatoes engineered to contain vaccine immunogens), transcutaneous skin patches, and nasal vaccines.

Clinical evaluation of vaccines is carried out through the DMID-supported Vaccine and

Treatment Evaluation Units (VTEUs). This program is a national and international resource for evaluating promising new vaccine and treatment candidates in phase I, II, and III clinical trials. Studies conducted by VTEUs have led to the development of novel approaches in preventing and controlling a number of important pathogens, including influenza A and B viruses, parainfluenza viruses, rotaviruses, *Haemophilus influenzae* type B, hepatitis B viruses, cholera, and *Bordetella pertussis*.

### *Emerging and Reemerging Infectious Diseases*

The threat posed by disease-causing microbes is expected to continue and even intensify in coming years. Infectious diseases have continued to emerge in recent years: diseases previously thought to be under control have undergone dramatic increases; new associations have been identified between chronic diseases and acute illness; opportunistic infections have arisen in immunosuppressed individuals; and previously unknown infections are now impinging on the public consciousness. Moreover, in recent months we have witnessed the deliberate mailing of spores of anthrax bacterium, demonstrating our nation's vulnerability to bioterrorism. In addition to anthrax, other potential agents of bioterrorism include smallpox virus, the bacteria that cause plague and tularemia, botulinum toxin, and filoviruses (e.g., Ebola virus).

Factors that may explain the emergence of a new infectious agent include changes in the microbial agent, in the human population, in its behavior in the vector population, or in the ecologic relationships between these factors. Currently, recognized infections with potential for further emergence or reemergence in more virulent forms, such as influenza, foodborne infections, hepatitis, and dengue, already cost the United States billions of dollars. DMID, by supporting a broad spectrum of basic, clinical, and epidemiologic research in infectious diseases, has the capacity to focus the research agenda to better understand the epidemiology, pathogenesis, and microbiology of emerging infectious diseases and ultimately to develop mechanisms of control and prevention. Examples of DMID activities in this area include the research programs in hepatitis C virus, foodborne diseases, Lyme disease, arboviruses such as West Nile virus, and infectious agents most likely to be intentionally released as a weapon of bioterrorism.

### *Antimicrobial Drug Resistance*

NIAID has initiated a number of research activities to address the increasingly important public health problem of antimicrobial resistance. The Institute is participating in the ongoing interagency task force for the development of a public health action plan for antimicrobial resistance. Developed by an interagency task force cochaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the NIH, *A Public Health Action Plan to Combat Antimicrobial Resistance* states issues, goals, and action items in surveillance, prevention and control, research, and product development. Its goal is to ensure a comprehensive, coordinated response by Federal agencies and industry in addressing this critical health issue. The action plan is available online at www.cdc.gov /drugresistance/actionplan/index.htm.

## Global Health

NIAID has developed comprehensive research plans for a number of infectious diseases of global importance, including TB, malaria, influenza, and STDs. Many of these activities focus on vaccine development. Genomics, microbial physiology, epidemiology and natural history, and development of improved diagnostics and therapies also are important areas of emphasis. Diseases of international health importance also present additional scientific and logistical challenges, such as access to endemic sites and populations. The Institute supports field-based research through investigator-initiated grants, disease-specific initiatives, and special programs, such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

Tropical and parasitic diseases are a major world health problem afflicting billions of people and causing millions of deaths annually.[1] In developing countries, they are impediments to social and economic progress. The vectors that transmit many of these diseases are common in the United States, raising the specter of their introduction and transmission domestically as well. There are no cures for many major parasitic infections, and the available chemotherapy often produces serious side effects. The Institute supports efforts to develop cost-effective, sensitive, and specific diagnostic tests; to develop new or improved chemotherapeutic approaches; to develop effective vaccines; and to control the transmission of disease by interfering with disease-bearing insect vectors. Investigations at the basic, clinical, and field levels are pursuing these efforts.

### *Tuberculosis*

TB is a chronic infection of an estimated one-third of the world's population, including approximately 10 to 15 million persons in the United States. TB is the leading cause of death in the world due to a single infectious agent and will claim 30 million lives during the coming decade unless efforts to control its transmission are improved.[2] The link between HIV and TB is anticipated to be an increasingly important factor in the spread of TB. Current research is focused on the development of improved diagnostics, treatment, and vaccine strategies to control and prevent disease. The identification of factors associated with the transmission and emergence of drug-resistant forms of TB is also a high-priority area. NIAID is actively engaged in helping to advance a national strategy for TB vaccine development. The Tuberculosis Research Unit (TBRU) supports an international, multidisciplinary team of collaborators to translate basic research findings into clinical studies.

### *Malaria*

Malaria remains the most important of the tropical parasitic diseases in terms of annual mortality. Infection with these protozoan parasites, which are transmitted by

[1] *Removing obstacles to healthy development: WHO report on infectious diseases,* 1999; www.who.int/infectious-disease-report.

[2] NIAID/NIH Workshop Report. *Blueprint for tuberculosis vaccine development.* B. Bloom, ed. March 5-6, 1998; World Health Organization (WHO). *Global tuberculosis control.* WHO Report 2001. Geneva, Switzerland.

mosquitoes, is a major public health problem in tropical and subtropical regions, where the disease exacts a heavy toll of illness and death. Although much effort has gone into controlling malaria in different parts of the world, initial successes have been reversed as a result of increased resistance of mosquitoes to standard insecticides, increased resistance of the malaria parasite to inexpensive and effective drugs, and changing epidemiologic and ecologic patterns resulting from economic development within malarious areas. The magnitude of the problem and existing barriers to control efforts require new approaches, including the use of vaccines, for prevention and treatment of malaria. Malaria is a high-priority research area for NIAID. Current research activities sponsored by NIAID include drug development, pathogenesis research, vaccine development, and epidemiology and vector control. NIAID's *Research Plan for Malaria Vaccine Development,* which describes the Institute's goals and plans for developing a malaria vaccine, can be viewed online at www.niaid.nih.gov/dmid/malaria/malvacdv/toc.htm.

### *Influenza*

Each year, 10 to 20 percent of Americans get sick with the flu (influenza). For most of us, fever, exhaustion, and aches and pains of the flu can be debilitating for 1 or 2 weeks, but for older persons and those with compromised immune systems, the flu can be much more serious. An estimated 100,000 hospitalizations and about 20,000 deaths occur each year from the flu or its complications.[3]

The major goal of NIAID's influenza program is to stimulate research leading to more effective approaches to control influenza virus infections. NIAID currently supports research on virus structure and function, viral pathogenesis, host response due to infection, understanding the natural history and ecology of zoonotic influenza viruses, vaccine development and testing, improving vaccine delivery, and drug discovery and clinical testing. NIAID's influenza program also develops diagnostic reagents against subtypes of avian influenza virus with high pandemic potential.

### *Sexually Transmitted Diseases*

STDs are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. The role of STDs as a risk factor for sexual transmission of HIV significantly raises the burden of this common group of diseases. DMID's research emphasis is on vaccine development and on clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STDs and conditions associated with having STDs, for example, pelvic inflammatory disease (PID), infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and the spread of HIV. NIAID also supports a topical microbicide research effort to prevent STDs; this effort encompasses basic, product development, and clinical research.

[3] www.niaid.nih.gov/newsroom/focuson/flu.htm.

### *Pathogen Genomics*

Advances in molecular biology have led to remarkably fast and accurate methods for sequencing the genomes of disease-causing microorganisms. Genome sequencing reveals the lineup of paired chemical bases that make up the pathogen's DNA, the language of life. The potential payoffs of sequencing pathogens are enormous. When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Once virulence genes are found, researchers can attempt to disable them. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains, such as the spread of a virulent or drug-resistant form of a pathogen in a susceptible population. Finally, understanding the genetic basis for both virulence and drug resistance also may help predict disease prognosis and influence the type and extent of patient care and treatment.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate sequence and functional data.

In summary, DMID supports a breadth of research activities on a variety of pathogens of importance in basic microbiology and infectious diseases.

# Division of Intramural Research

The Division of Intramural Research (DIR) (www.niaid.nih.gov/dir) is home to NIAID's renowned laboratories and clinical research programs, which cover a wide range of biomedical disciplines related to immunology, allergy, and infectious diseases. DIR scientists conduct basic laboratory research in the areas of virology, microbiology, biochemistry, parasitology, epidemiology, mycology, molecular biology, immunology, immunopathology, and immunogenetics.

DIR also conducts more than 80 clinical protocols at any given time, using the facilities of the Warren Grant Magnuson Clinical Center on the NIH campus. Clinical Center physician-scientists treat patients with a variety of diseases, including AIDS, vasculitis, immunodeficiencies, host defense defects, unusual fungal infections, asthma, allergies, various parasitic diseases, and disorders of inflammation. Frequently, patients participate in studies of new and promising treatments or diagnostic procedures derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

## Scientific Resources

Each of the 15 DIR laboratories (www.niaid.nih.gov/dir/labs.htm) contains state-of-the-art equipment that is augmented by the expertise and services provided by 5 supporting branches. DIR scientists share access to sophisticated instruments and techniques, such as peptide synthesis, sequence analysis of proteins, mass spectroscopy, confocal microscopy, and four-channel flow cytometry. DIR has facilities for breeding transgenic and gene-targeted (knockout) mice and provides other animal care services, including extensive in-house animal breeding and holding facilities, oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities are maintained in Bethesda, Maryland, and at the DIR laboratories in Hamilton, Montana. In addition, biosafety-level-three facilities for both laboratory and animal studies are available at those locations.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of the NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine, and links DIR researchers in the Maryland locations of Bethesda, Rockville, the Frederick Cancer Research and Development Center, and the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are

much faster and more dependable than the local Internet service-provider connections.

## Immunology Research

In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Much of the research focuses on the B and T lymphocytes, which react to foreign organisms that have entered the body. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, they help us understand and develop effective treatments for immunodeficiency diseases in which the lymphocytes are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Current projects include the following:

- Role of cytokines in the pathogenesis and treatment of autoimmune diseases,
- Structural analysis of T-cell receptors, and
- Gene therapy for immunodeficiencies.

## Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. DIR studies include the following:

- Cytokine profiles of allergic diseases,
- Tolerance studies for asthma, and
- Efficacy of a soluble interleukin-4 receptor in treating asthma.

## Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, the host response to infection, vector biology, and chemotherapeutics. Studies of the organisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, Lyme disease, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies reveal new targets for public health interventions. DIR investigators also are studying potential infectious etiologies of chronic diseases. Several infectious agents, such as hepatitis C virus, human

papillomavirus, and *Chlamydia pneumoniae*, have been associated recently with chronic illnesses. Examples of ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy,
- Pathogenesis of transmissible spongiform encephalopathies, and
- Genetics of drug resistance, antigenic variation, and disease severity in malaria.

## Vaccine Research

DIR researchers are developing several new and novel vaccines, such as those that might be able to immunize people against more than one disease at the same time. Another example of a novel vaccine is the transmission-blocking vaccine for malaria, which would prevent a mosquito that had just bitten a malaria-infected person from transmitting the malaria parasite to other individuals. Studies are under way to develop vaccines against pathogenic flaviviruses, especially the dengue virus, which may lead to the development of vaccine candidates for the newly emergent West Nile virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR.

## Division of Intramural Research Laboratory Review Process

| Step 1<br>Scheduling and Approval | Step 2<br>Team Selection | Step 3<br>Preparation for Site Visit | Step 4<br>Site Visit | Step 5<br>Site Visit Report and Recommendations | Step 6<br>Implementation and Recommendations | Step 7<br>Followup Report |
|---|---|---|---|---|---|---|
| **Division of Intramural Research (DIR)**<br>Director, DIR, approves date of scheduled review. | Director, DIR, in consultation with Director, NIAID, recommends slate of term appointment and ad hoc candidates for Review Team membership. | DIR laboratory(ies) prepares and forwards research and administrative summaries to Director, DIR, for review. Director, DIR, prepares Review Team interview schedule and forwards materials to Review Team. | Research presentations are made by laboratory staff, and Review Team conducts interviews of selected staff. | Laboratory Chief attends site visit report presentation and has opportunity to comment on draft report of his or her laboratory. | Director, DIR, and Deputy Director, DIR, meet with laboratory staff to discuss report and BSC recommendations. On the basis of the action plan developed by the Director, DIR, laboratory implements the appropriate recommendations provided by Review Team. | BSC recommendations and Director, DIR, response are sent to Deputy Director for Intramural Research, NIH, who obtains further review by selected Scientific Directors of other ICDs. Director, DIR, reports about BSC at next meeting and to the National Advisory Allergy and Infectious Diseases Council. |
| **Board of Scientific Counselors (BSC)** | Chairperson, BSC, selects Review Team members. | BSC and Review Team members review materials prepared by DIR laboratory(ies). | Review Team hears presentations and conducts interviews of laboratory staff. BSC develops a preliminary report on site. | BSC preliminary report is presented to Director, DIR, Director, NIAID, and Deputy Director for Intramural Research, NIH, at the Executive Review Session. Final, comprehensive report is typed, edited, and forwarded to Director, DIR, for review and action. | | |

# Dale and Betty Bumpers Vaccine Research Center

The Dale and Betty Bumpers Vaccine Research Center (VRC) (www.vrc.nih.gov) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of the VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated 5 million new HIV infections each year, and in 2001, HIV/AIDS was the fourth overall leading cause of mortality worldwide, resulting in an estimated 3 million deaths.[1] Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Accordingly, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that may lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, the VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

The impact and importance of vaccines cannot be overstated. Vaccines are powerful public health tools that provide safe, cost-effective, and efficient means of preventing morbidity and mortality from infectious diseases. They have revolutionized the control of infectious diseases, virtually eliminating polio, smallpox, and measles; however, an effective vaccine against HIV poses unique obstacles. HIV strains worldwide display tremendous genetic diversity that may limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce

[1] UNAIDS and World Health Organization. *AIDS epidemic update*, December 2001. www.unaids.org/epidemic_update/report_dec01/index.html#full.

effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

## Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this process has been successful for numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology is now emerging that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance. By having diverse components of vaccine research, development, production, and evaluation readily accessible at one site, along with a group of committed investigators with diverse skills but a common goal, the VRC has embarked on a comprehensive and systematic approach to vaccine development.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, will be established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, the VRC hopes to advance the science of vaccine development.

## Research Goals and Objectives

The VRC has four broadly encompassing research goals, each of which has multiple subparts. The goals are as follows:

- Goal 1: Scientifically design and develop effective vaccine candidates
  - Use knowledge of the HIV envelope structure to design immunogens that elicit potent virus-neutralizing antibodies through a program of rational structure-based design and screening of immunogens
  - Develop and optimize gene-based vaccine platforms that elicit broad and potent cell-mediated and humoral immunity
  - Use state-of-the-art methods in genomics and bioinformatics to advance vaccine development
- Goal 2: Evaluate and optimize the immune response generated by candidate vaccines
  - Identify and develop validated, reproducible methods to quantitate

vaccine-induced immune responses in humans and primates

- Identify vaccine candidates and immunization strategies that enhance potency, antigen presentation, and immunogenicity

- Develop rational use of the primate model to assess vaccine strategies and define immune correlates

- Goal 3: Advance the most promising vaccine candidates into human clinical trials

  - Develop the infrastructure to produce and test vaccine products

  - Conduct clinical evaluation of candidate vaccines

  - Evaluate preventive vaccine candidates in clinical protocols of therapeutic immunization

- Goal 4: Create the necessary infrastructure for translating basic research to the clinic

The construction of the Vaccine Development Facility (VDF) is a high priority for the VRC. The VDF will manage production of multiple vaccine candidates originating from the VRC. To achieve this objective, the VDF will function in concert with the Vaccine Production Laboratory located at the Bethesda campus in transferring new vaccine technology for pilot-scale production of clinical trial material. The VDF will be designed as a pilot plant in Frederick, Maryland, with an anticipated completion date of early 2004. Vaccines produced at the VDF will support phase I and II clinical trials. In addition, the facility will incorporate design features that will allow conversion to larger scale operations capable of supporting phase III trials, if necessary.

## Basic Research

### *Acquired Immunodeficiency Syndrome*

The VRC aims to develop vaccine candidates that will induce effective humoral (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Recent data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program will explore basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at the VRC will apply this knowledge toward the design of vaccines. A program in virus structural biology will explore the rational design of vaccines that can induce potent virus-neutralizing antibodies. Development of candidate vaccines will focus on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered using immunization with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided

by these candidate vaccines. Such preclinical animal testing is closely integrated with the VRC's basic science programs to provide information for iterative improvements in the development of new candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV will be guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. Reproducible, validated assays to measure T-cell function and virus particle reduction will be developed and applied to animal studies and human clinical trials. In this way, scientists can determine how effectively the candidate vaccine protects against infection or disease. Preclinical studies in small animals and primates will evaluate vaccine dose, formulation, and delivery route and will address the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be closely integrated with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

### *Ebola*

The Ebola virus is associated with an aggressive course of infection, hemorrhagic fever, and a high mortality rate, particularly for the Ebola Zaire subtype. Because the natural reservoir for Ebola virus is unknown, traditional public health measures to prevent future outbreaks are limited, thus increasing the urgency for development of an effective vaccine. Previously, it had been shown that immunization with DNA encoding Zaire-subtype glycoprotein (GP[Z]) yielded a significant humoral protective response in guinea pigs. The VRC carried out additional studies and determined that a prime-boost strategy, with naked DNA as prime (initiation of an immune response) and recombinant adenoviral vector as boost (enhancement of the initial immune response) substantially enhanced the immune response.

The VRC will continue to develop and test multivalent vaccines to evaluate their protection against multiple hemorrhagic fever pathogens of natural or deliberate infections.

## Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general, and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, the VRC will combine traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach will promote an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, the VRC will study the ability of

vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T-cell memory that play a role in protection against HIV. Such data can then be applied to the development of therapeutic and preventive vaccines.

The VRC will actively collaborate with intramural and extramural scientists and facilitate the movement of ideas from the broader community into clinical trials. The VRC will maintain close ties with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials is already established. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, the VRC also will interact with the pharmaceutical industry, in which there is a large capacity for, and experience in, product development and distribution. Therefore, the VRC will fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

## Human Clinical Trials and Licensure of an AIDS Vaccine

The VRC will work closely with its scientific collaborators and with the Food and Drug Administration to discuss the potential for expedited approval of AIDS vaccines. The carefully considered use of surrogate end points (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate end points can accrue from well-designed trials, and this information can be applied to the design of future trials.

# Global Health

The NIAID research mission in infectious and allergic diseases is of global importance. When combined, these conditions are the most common causes of preventable human illness and death around the world. Recent concern about emerging and reemerging infectious diseases and the anthrax biological weapon attacks of October 2001 further reinforced the importance and added new dimensions to NIAID-supported research in improving early diagnosis, prevention, and control of these pathogens. Formal recognition of the importance of international research dates back to the International Health Act (1960), which gave the Secretary of Health and Human Services—formerly the Secretary of Health, Education, and Welfare—the authority to conduct research activities outside the United States, provided that the activities were beneficial to the health of U.S. citizens. This authority has been delegated to the NIH and to NIAID. The Public Health Service Act of 1988 (Public Law 100-607) created new HIV/AIDS authorities for the NIH. Subsequently, the NIH Revitalization Act (1993) gave NIAID specific authority to conduct research on tropical diseases that disproportionately affect populations in resource-poor and economically restructuring countries.

In May 2001, NIAID announced its Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis. The Global Plan provides short-, medium-, and long-term objectives for treating, preventing, and controlling these diseases by building on the Institute's strong foundation in infectious disease research.

For carrying out its international research activities, NIAID uses the following five approaches.

## Intramural Research Training and Collaborative Research

NIAID laboratories located in the Bethesda/Washington area and Hamilton, Montana, are a significant source of research training for postdoctoral non-U.S. scientists at formative stages in their careers. Under most circumstances, the NIAID laboratory provides stipends for the visiting scientists. The research training experience frequently leads to long-term intramural or extramural collaborations once the scientists return to their home countries. In FY 2001, the largest numbers of NIAID foreign scientists were from China, Italy, France, Japan, India, Russia, Australia, Germany, Canada, Korea, and Brazil.

NIAID laboratories become substantially involved in international research projects when these activities are essential to their research efforts. Funding ordinarily comes from the laboratory's regular budget and, for that reason, is not usually a major source of financial support. Exceptions may occur when the intramural laboratory is part of a consortium and/or the laboratory is able to secure extra-budgetary funding.

Since 1989, the NIAID Laboratory of Parasitic Diseases has been working with scientists and physicians at the National School of Medicine of Mali, located in Bamako, West Africa, to develop the Malaria Research and Training Center (MRTC). The Center has developed into a well-equipped, highly productive facility in which the research is planned, directed, and executed by Malian staff. Funding comes from a number of U.S. and international agencies, including several NIAID-funded U.S. universities. In collaboration with the NIH

National Center on Minority Health and Health Disparities, the Fogarty International Center (FIC), and the University of Maryland, NIAID's Laboratory of Parasitic Diseases developed a training program for young U.S. scientists and medical students to gain experience in an African setting. The MRTC also recently dedicated a new laboratory research facility and dormitory.

Building on the experience in Mali, NIAID is now developing the International Center for Excellence in Research (ICER) program, which has the objective of using longstanding intramural research to achieve long-term, sustainable collaboration and to attract extramural competitive funding. ICER projects are presently under development in India (tropical diseases), Papua New Guinea (malaria), and Uganda (HIV/AIDS).

## Domestic Research Awards with a Foreign Component

NIAID funds the vast majority of its international research indirectly through competitive domestic extramural research awards that have a foreign component. Special emphasis programs have been developed in tropical medicine, emerging infectious diseases, HIV/AIDS, and tuberculosis to take advantage of research opportunities overseas in countries with a disproportionate burden of these diseases.

The NIAID International Centers for Tropical Disease Research (ICTDR) network is the earliest and most mature of these special programs. The ICTDR network consists of (1) Tropical Disease Research Units (TDRUs), which are U.S. institutions conducting multidisciplinary research relevant to the treatment, prevention, or control of tropical diseases, (2) the International Collaboration in Infectious Disease Research (ICIDR) program, which makes awards to U.S. institutions to engage in substantial international collaboration with overseas institutions in tropical medicine and emerging infectious diseases, (3) NIAID intramural laboratories active in tropical medicine and infectious disease research, (4) additional U.S. institutions with a critical mass of tropical and emerging infectious disease research, and (5) Tropical Medicine Research Centers, which provide direct funding to overseas centers of excellence. In FY 1999, NIAID formally linked the ICIDR program with the FIC Assistance in Building Capacity (ABC) institutional research training program.

Initiated in 1994, the NIAID Tuberculosis Prevention Research Center has operated through a research contract with Case Western Reserve University to coordinate a consortium of U.S. and international (Brazil and Uganda) institutions to conduct a range of high-priority research projects that range from basic research to the development and evaluation of new or improved diagnostic tests, drugs, and vaccine candidates.

NIAID has supported a series of special programs for research on HIV/AIDS and related problems outside the United States since 1985. In FY 2000, NIAID restructured and expanded these programs into the separate but complementary HIV Prevention Trials Network (HPTN) and HIV Vaccine Trials Network (HVTN). The HPTN currently consists of 15 U.S. and 14 international sites. The HVTN is composed of 18 U.S. and 11 international sites. For a listing of the

HVTN/HPTN U.S. and international locations, see page 31.

## Foreign Awards

NIAID and the NIH accept investigator-initiated research proposals from foreign scientists and permit foreign scientists to respond to most program announcements (PAs) and requests for applications (RFAs). To be funded, foreign applications must receive a competitive peer-review score and be approved by the National Advisory Allergy and Infectious Diseases Council (NAAIDC) on the basis of their uniqueness and/or program relevance. Foreign scientists also may be eligible to compete for NIAID research contracts when U.S. institutions cannot carry out the project (e.g., pertussis vaccine trials in Italy and Sweden) or when the domestic applications are not responsive to the solicitation.

Historically, foreign awards have accounted for about 1 percent of the NIAID budget. As basic research results in new or improved products that require evaluation in populations with heavy burdens of disease, this amount is expected to increase. Furthermore, long-term NIAID investment in collaborative research has resulted in the development of overseas sites capable of independent research. The establishment of the Tropical Medicine Research Center Program a decade ago was a reflection of this phenomenon. In FY 2001, NIAID launched the Comprehensive International Program for Research on AIDS (CIPRA). CIPRA represents a major departure from other NIAID international programs in that it provides direct funding to a consortium of HIV/AIDS investigators in the host country to carry out research of high national priority. A second innovation is that CIPRA will provide planning grants and infrastructure strengthening and training awards in addition to traditional funding to conduct research. The initial CIPRA awards were planning grants to groups in China, Peru, the Russian Federation, Trinidad and Tobago, and Zambia.

## Official Bilateral Programs

In addition to regular scientific channels, the United States often develops formal, bilateral scientific agreements with foreign governments or organizations at the Presidential, Department of Health and Human Services (DHHS), NIH, or NIAID level. NIAID carries out these programs with budgeted funds unless special or supplementary funds are made available. During FY 2001, NIAID actively participated in bilateral programs involving Brazil, China, France, the Republic of Georgia, Germany, India, Italy, Japan, Russia, South Africa, and Taiwan. Of particular interest is the U.S.-Japan Cooperative Medical Sciences Program (USJCMSP), which consists of committees of senior scientists and panels of experts in high-priority diseases of the Pacific Basin. Both the Joint USJCMSP Committee and Joint Panels meet annually, alternating countries in conjunction with scientific conferences. The USJCMSP also has organized annual workshops on emerging and reemerging infectious diseases in the Pacific Basin at different sites in the region. Active priority areas are AIDS, acute respiratory infections, cholera and other bacterial enteric diseases, environmental mutagenesis and carcinogenesis, infectious hepatitis, immunology, leprosy/tuberculosis, nutrition, parasitic diseases, and viral diseases.

## International Agencies and Organizations

NIAID has joined with other organizations to enhance scientific collaborations in combating infectious diseases. Examples include the Presidential Millennium Vaccine Initiative; the Global Alliance for Vaccines and Immunization (GAVI); the Multilateral Initiative on Malaria in Africa (MIM); the International Cooperative Biodiversity Groups Program; and the DHHS-State Department BioTechnology Engagement Program (BTEP) and the Civilian Research and Development Foundation (CRDF), both of which provide support to scientists in the Newly Independent States to conduct collaborative research on problems of public health importance.

NIAID staff members also participate on the scientific boards of and as consultants to the World Health Organization, the Pan American Health Organization, and the U.S. Agency for International Development.

# Acquired Immunodeficiency Syndrome (AIDS)

Significant progress has been made in HIV/AIDS research since 1981 when AIDS first emerged as a global infectious disease. Research has led to a better understanding of the structure of HIV and how HIV attacks the immune system, and the role of the immune system in controlling HIV infection and how to intervene therapeutically. Potent therapeutic regimens, commonly referred to as highly active antiretroviral therapy, or HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and in decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected people in the United States and has led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the HIV/AIDS pandemic continues to rage around the world, with 40 million people (37.2 million adults and 2.7 million children) living with the disease. In 2001, 3 million people died from AIDS, and 5 million people were newly infected with HIV. More than 95 percent of new HIV infections occur in the developing world, with 68 percent occurring in sub-Saharan Africa and 16 percent in Southeast Asia. Most of these new infections are in young adults, with an increasing number among women.[1] In the United States, close to 900,000 people are living with HIV/AIDS, and each year 40,000 new infections occur, of which more than one-half are in individuals younger than 25 years of age.[2]

Since the beginning of the epidemic, NIAID's comprehensive research program has been at the forefront in the fight against AIDS. NIAID supports a broad array of domestic and international HIV/AIDS research programs and collaborates with more than 40 countries through investigator-initiated research grants and multicenter prevention, vaccine, and therapeutic research networks.

With a growing number of research programs and initiatives, NIAID is poised to tackle new research challenges and the changing demographics of the HIV/AIDS epidemic. For example, NIAID initiated the Comprehensive International Program for Research on AIDS (CIPRA) (www.niaid/daids/cipra) in 2001 to address research needs in developing countries. CIPRA is a grant program designed to provide long-term support to developing countries to plan and implement comprehensive HIV/AIDS prevention and treatment research agendas relevant to their populations, to enhance the infrastructure necessary to conduct such research, and to participate in collaborative, multicenter clinical trials. In 2001, five awards were made to research institutions in China, Peru, Russia, Trinidad, and Zambia.

## Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV subtypes is the ideal prevention strategy and NIAID's highest priority. To accelerate vaccine development worldwide, NIAID established the HIV Vaccine Trials Network (HVTN). The HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate HIV vaccines. The HVTN has 18 U.S. sites and 11 international sites. For a listing of the HVTN locations, see page 31. NIAID's HIV vaccine efforts are described in more detail in Vaccine Research and Development on page 86.

## Nonvaccine Prevention Research

To control the HIV epidemic, new and more effective methods and strategies are needed for preventing HIV infection. Until a highly efficacious vaccine is developed that can be widely distributed and used, or even a partially protective vaccine, control of the epidemic will require a combination of prevention approaches. NIAID established the HIV Prevention Trials Network (HPTN) to develop and test promising nonvaccine strategies to prevent the spread of HIV/AIDS. The HPTN includes 15 domestic sites and 14 international research sites. (See the map on page 31.) The HPTN evaluates the efficacy of promising biomedical and behavioral interventions for the prevention of HIV, including the following:

- Drugs or vaccines that are practical and easy to use to prevent mother-to-infant HIV transmission, including prevention during breastfeeding;
- Microbicides to prevent sexual transmission of HIV (see Topical Microbicides under Sexually Transmitted Diseases on page 103);
- Antiretroviral therapy (ART) that may reduce the spread of HIV from infected persons to their sexual partners;
- Measures to control other sexually transmitted diseases and thereby decrease the risk of co-infection with HIV;
- Interventions to reduce behavior that exposes people to HIV; and
- Programs to curb the spread of HIV by reducing intravenous drug abuse.

NIAID-funded research through the HPTN and other sources of support has led to important scientific advances that increase our understanding about the transmission of HIV. These findings provide a foundation for developing and testing innovative prevention strategies. Recent findings include the following:

- Data establishing the continued benefit and safety of giving nevirapine to mothers and their newborn infants to reduce perinatal HIV transmission through 18 months, even in a breastfeeding population;
- Identification of a direct correlation between the level of HIV in the blood and the rate of transmission of HIV through heterosexual sex;
- Stronger evidence that early circumcision may reduce men's risk of HIV acquisition during unprotected sexual contact later in life; and
- Evidence associating genital herpes infection with an increased susceptibility to HIV.

## Therapeutics

The increased life expectancy of HIV-infected individuals as a result of HAART has resulted in more individuals living with the disease, as well as a host of complications resulting from the therapeutic regimen. These complications include the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by HAART. Thus, there continues to be an urgent need for

new therapeutic entities and approaches to expand the number and clinical benefit of currently approved therapies. NIAID's therapeutics research programs and networks are focusing on these issues. Examples of HAART research studies are provided below.

NIAID researchers have found a beneficial effect in the immune response when antiretroviral therapy was interrupted repeatedly. This approach has important implications for the long-term use of antiretrovirals and could decrease both the cost and side effects of treatment. Additional research on treatment interruption is ongoing. In addition, NIAID is launching a new study titled Strategies for Management of Anti-Retroviral Therapies (SMART). (Additional information on SMART is located in the Drug Research and Development section of Selected Scientific Areas of Interest on page 101.) This study will determine which of two common HIV treatment strategies results in a better outcome over time. SMART is among the first long-term studies of its kind and is being conducted through the Community Programs for Clinical Research on AIDS (CPCRA).

A major goal of NIAID intramural researchers and their collaborators is to discover new therapies for AIDS that are less expensive or less toxic than current therapies and, therefore, have the potential for more widespread use. Several new approaches are under study in NIAID's Division of Intramural Research (DIR). For some HIV-infected patients whose plasma levels of virus have fallen to undetectable levels while on HAART, it may prove feasible to move from a continuous HAART regimen to intermittent therapy in which an individual discontinues then resumes HAART in a preplanned cyclic fashion. This cyclic approach to treatment, known as structured intermittent therapy, might enable an HIV-infected person to have regular HAART-free periods while maintaining a minimal viral load and adequate levels of CD4+ T cells.

DIR researchers recently completed a pilot study in which 10 HIV-infected individuals already taking effective drug therapy received repeated cycles of 7 days on HAART, followed by 7 days off HAART, for up to 68 weeks. In this proof-of-concept study, the regimen of structured intermittent therapy maintained suppression of both the presence of viral particles in the blood and HIV replication in reservoir sites while preserving CD4+ T-cell counts.[3] In addition, study volunteers experienced a decrease in important toxicity parameters and significantly lower cholesterol and triglyceride levels, which are often abnormally elevated in patients on HAART. Thus, short-cycle intermittent HAART may reduce the cost and toxicity of antiretroviral therapy by reducing the total time on HAART by one-half. This approach has particular applicability in resource-poor settings where access to therapy is limited by the cost of antiretroviral agents. Larger clinical trials are under way to address the efficacy and impact of this short-cycle intermittent therapy.

While HAART has dramatically improved the clinical outcome for many HIV-infected patients, the associated cost, toxicity, and development of drug resistance underscore the need for additional therapeutic strategies. Strategies aimed at enhancing the ability of the immune system to fight HIV infection are under investigation by NIAID intramural scientists and others as potential supplements to antiretroviral therapy. These immune-based

strategies include treatments that stimulate or suppress a particular part of the immune system, infusion of additional immune system cells, and therapeutic immunizations. NIAID's long-term basic research into the function of interleukin-2 (IL-2) in the immune system and clinical studies of its safety and efficacy for HIV therapy have led to promising results. Randomized phase III clinical studies by NIAID intramural investigators, as well as two large international studies, are ongoing to clarify the effect of IL-2 on viral load and CD4+ counts and to assess long-term clinical outcomes.[4]

# Malaria

Malaria, a serious disease caused by a parasite transmitted by a mosquito, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Because of variations in the parasite species that cause malaria, the development of a successful vaccine has been difficult. Globally, malaria causes more than 1 million deaths each year, primarily in children. According to the World Health Organization (WHO), almost 300 million clinical malaria cases occurred in 1998,[5] and there were an estimated 1.09 million deaths and 45 million lost disability-adjusted life years (DALY) in 1999.[6] The situation is worsening, as drug-resistant strains of the most virulent form of the malaria parasite, *Plasmodium falciparum*, have spread to most endemic regions.

Malaria research at the NIH dates back to the 1930s, a time when malaria was a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID activities in malaria include a broad portfolio of research on parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector control, conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories, and overseas.

NIAID has a large intramural program dedicated to malaria vaccine development. (See the text box on page 61.) In addition, intramural investigators are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, they are characterizing molecules that determine the *Plasmodium* parasites' response to chloroquine and quinine, with a view toward new therapeutic strategies and diagnostics for the detection of drug-resistant malaria. To understand the factors that determine the severity of malaria, NIAID investigators are studying how hemoglobin C and hemoglobin S (sickle-cell hemoglobin) protect children from severe and fatal complications of *P. falciparum* malaria. Antigens are substances that provoke immune responses. NIAID studies of the mechanisms by which parasites coordinate the silencing and activation of certain genes that are responsible for antigenic variation in malaria are clarifying how parasitized red blood cells avoid destruction by the human immune system. To further their discovery of a novel feeding channel through which malaria parasites uptake nutrients while infecting red blood cells,[7] NIAID scientists are evaluating these channels as potential new targets for future antimalarial vaccines or chemotherapies.

To complement laboratory-based research, NIAID-supported investigators are conducting clinical and field-based studies of malaria in endemic regions, including Brazil, Cameroon, Ghana, Indonesia, Malawi, Mali, Papua New Guinea, and Thailand.

In 1997, the Institute developed a multiyear plan to accelerate research on malaria vaccine development. The plan emphasizes the following:

- Improved access to well-characterized research materials,
- Discovery and preclinical testing of new vaccine candidates,

- Production and evaluation of candidate vaccines, and

- Clinical research and preparation for clinical trials in endemic areas.

As early steps in implementing this plan, NIAID established a repository of well-characterized malaria research reagents, expanded efforts to sequence the genomes of human and rodent malaria parasites and, more recently, that of the mosquito vector *Anopheles gambiae*, and expanded current malaria vaccine production and evaluation efforts through collaborations between intramural and extramural scientists. Some noteworthy aspects of NIAID-supported research carried out in FY 2001 include the following:

- Sites in Ghana and Mali in West Africa, supported by contracts under the Malaria: Clinical Research and Trial Preparation Sites in Endemic Areas initiative, continued to develop research infrastructure and carry out clinical and field studies. Current studies are looking at entomological aspects of malaria transmission, the epidemiology and burden of disease, and factors influencing the clinical presentation and pathogenesis of malaria. The onsite resources will support multidisciplinary clinical and field-based research necessary to facilitate conduct of clinical trials of interventions, particularly vaccines against malaria.

- NIAID recently awarded a 7-year contract to Science Applications International Corporation (SAIC) for malaria vaccine production and support services. The contract is supporting the transition of promising malaria vaccine candidates from discovery in the laboratory through preclinical evaluation and production to clinical trials.

- NIAID continues to collaborate and coordinate with other Federal agencies, such as the U.S. Agency for International Development, the Centers for Disease Control and Prevention, and the Department of Defense, to accelerate research and development of malaria vaccines. NIAID also is working closely with nongovernmental agencies for the same purpose. Under a Memorandum of Understanding (MOU) established in FY 2000, NIAID and the Malaria Vaccine Initiative (MVI) have established strategic joint efforts to support promising malaria vaccine development efforts. NIAID is a founding member of the Multilateral Initiative on Malaria (MIM), a consortium of research-funding agencies created to improve global collaborations in malaria research. MIM works closely with WHO's Roll Back Malaria Program and others to ensure that research findings are applied to improve malaria control.

## NIAID Malaria Vaccine Development Unit Dedicated in Spring 2001

The Malaria Vaccine Development Unit (MVDU) is a new NIAID initiative developed to respond to the global need for a vaccine against malaria. Located in Rockville, Maryland, the MVDU has facilities for production of malarial proteins (the key component of the vaccine) and subsequent protein purification and analysis. MVDU researchers are working to determine optimal formulations of malarial protein antigens and adjuvants in animal models to identify immunologic tests that show a correlation with protective immunity and to explore synergistic responses to different parasite antigens. In addition, the MVDU includes an outstanding clinical team to oversee and conduct human clinical trials.

The Unit is developing two types of malaria vaccines on the basis of two different strategies for malaria control. The first, called a blood-stage vaccine, is designed to elicit an effective immune response aimed at the parasite after it enters the blood of a human host, thereby protecting that individual from malarial disease. The second, called a transmission-blocking vaccine, is designed to stop the transmission cycle of the malaria parasite by inducing the production of antibodies in the infected human that would be ingested along with the parasites during a mosquito bite. The antibodies act by inhibiting the parasite's development within the mosquito itself and thereby prevent the onward transmission of the parasites.

The most advanced blood-stage vaccine candidate in development within the MVDU is made from a protein called MSP-1 of *Plasmodium falciparum*. The MVDU has been evaluating an antigenic portion of this molecule produced by collaborators at Novavax. Two recent studies have shown that monkeys can be protected against P. falciparum infection after immunization with this antigen.* Clinical grade material will be ready for a phase 1 trial in early 2002.

The MVDU's transmission-blocking vaccine candidate is an antigen of *Plasmodium vivax* called Pvs25. MVDU scientists, using **c**urrent **G**ood **M**anufacturing **P**ractices (cGMP), completed production and purification of Pvs25, the first antigen to be tested in the MVDU, using the Walter Reed production facility at Forest Glen, Maryland. A wide range of requisite preclinical studies are being completed on this protein, along with a number of studies in mice and nonhuman primates to determine a formulation suitable for human clinical trials. When the appropriate studies have been completed, an investigational new drug application will be prepared and submitted to the Food and Drug Administration for a phase I trial of the selected formulation. Assuming no regulatory difficulties, a phase I trial is planned for the spring of 2002.

The MVDU clinical trials component anticipates conducting many of the phase I clinical studies in the NIH Clinical Center. When vaccine formulations are found to be safe and immunogenic, further phase I and phase II testing will be in collaboration with colleagues at the NIAID-supported Malaria Research and Training Center in Mali, West Africa, or at other suitable field sites.

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* Stowers AW et al. Efficacy of two alternate vaccines based on *Plasmodium falciparum* merozite surface protein 1 in an Aotus challenge trial. *Infect Immun* 2001;69(3):1536-1546.

# Tuberculosis

NIAID plays a lead role in the NIH tuberculosis (TB) research program. From 1992 to 2001, NIAID has continued to increase its TB research portfolio. This action is in response to ongoing concern about increasing worldwide case rates and the development of multi-drug-resistant strains of *Mycobacterium tuberculosis*, the pathogen that causes TB. The World Health Organization (WHO) estimates that there are approximately 8 million new cases and 2 million deaths from TB each year, making TB the leading infectious cause of death from a single pathogen worldwide. It kills more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M. tuberculosis*, and 1 in 10 of these individuals will likely develop active TB disease. Moreover, it is estimated that between 2000 and 2020, nearly 1 billion people will be newly infected, 200 million people will get sick, and 35 million people will die from TB if we do not significantly improve our ability to control this disease.[8] NIAID supports a broad TB research program, primarily through its extramural Division of Microbiology and Infectious Diseases (DMID), with particular emphasis on the following areas:

- Basic biology and virulence of *M. tuberculosis*, host-pathogen interaction, and immunology of TB in animal models and humans;
- Research into the various stages of TB, especially persistent, asymptomatic infection with *M. tuberculosis* (latency) and reactivation of TB from this state;
- Development and testing of vaccines, improved chemotherapeutics, and diagnostics;
- Development of improved tools for epidemiologic studies; and
- Mycobacterial genomics and postgenomic analyses.

NIAID also supports related whole genome-sequencing efforts, including the sequencing and annotation of genomes of pathogenic mycobacteria such as *M. tuberculosis* (completed) and *M. avium* (in progress) and model organisms such as *M. smegmatis* (in progress). The availability of these genome sequences will improve our understanding of the basic biology and pathogenesis of mycobacterial diseases and stimulate development of new diagnostic tools, vaccine candidates, and drug therapies.

Contracts issued by DMID and the Division of Acquired Immunodeficiency Syndrome (DAIDS) are used to support and promote research in TB. The contract mechanism provides *M. tuberculosis*-derived research reagents, an animal model TB candidate vaccine and a drug-screening service, and the establishment of a multidisciplinary Tuberculosis Research Unit. NIAID also has established a contract to assist with technology transfer for potential commercialization of new drug discoveries for TB and participates in a newly formed public-private partnership—The Global Alliance for Tuberculosis Drug Development—with WHO, the Rockefeller Foundation, and other international organizations dedicated to bringing new therapeutic advances forward in the absence of industrial sponsorship. NIAID has established a chemical database to serve as a reference for these drug-screening results and to stimulate the design and synthesis of

new candidate drugs. A clinical trials network is evaluating existing drugs approved for other clinical indications, and the National Cooperative Drug Discovery Groups—Opportunistic Infections is searching for new drug targets and candidate lead compounds against *M. tuberculosis*. Increased funding through Small Business Innovation Research grants also has promoted development and evaluation of new diagnostic tests for *M. tuberculosis*.

The Division of Allergy, Immunology and Transplantation (DAIT) supports a number of individual research projects concerned with basic mechanisms of immunity to *M. tuberculosis*. DAIT's research goals and objectives on *M. tuberculosis* are as follows:

- To understand how the immune system recognizes and responds to bacteria hidden within host cells, such as *M. tuberculosis*, encourage research on antigen presentation and stress molecule induction as they relate to activation of cell-mediated immunity to intracellular pathogens;

- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;

- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and

- Support research on the identification of genes expressed in immune responses to mycobacterial infection, especially soluble proteins that might be used in vaccination or in treatment of the disease.

Research topics include T lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M. tuberculosis* infection, and the function of biological oxidants in protective immune processes.

DAIT supports several projects that focus on hepatitis C, TB, malaria, and HIV. Under the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines program, DAIT also supports the HLA Ligand/Motif Online Database, a web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands, which is now available online. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and self-proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs that will facilitate their research efforts. Support is provided under a NIAID contract to the University of Oklahoma. The web site address is http://hlaligand.ouhsc.edu.

The NIAID Tetramer Facility produces peptide-MHC reagents for T-cell detection and has provided more than 750 tetramers to investigators worldwide. Requests include reagents for the study of T-cell responses relevant to many vaccine topics, including intracellular bacterial, viral, and parasite infections, autoimmune diseases, and basic immunobiology. More information on this facility can be found at www.niaid.nih.gov/reposit/tetramer/index.html. The National Cancer Institute also provides funding for the Tetramer Facility.

The Division of Intramural Research (DIR) conducts basic research in *M. tuberculosis* at both the Bethesda, Maryland, and the Hamilton, Montana, campuses of NIAID. After contributing to the determination of the genomic sequence of *M. tuberculosis*, DIR investigators are now focusing on unraveling the functions of its various genes. This knowledge is critical to new drug and vaccine development and to understanding the molecular mechanisms involved in the emergence of drug resistance.

DIR's studies of the biochemical, immunologic, and genetic factors that contribute to human susceptibility and pathogen fitness have yielded many important findings that have enhanced the diagnosis and treatment of mycobacterial diseases. Using the most modern technologies, DIR scientists also are working on a number of different approaches to understand how current antitubercular chemotherapy works. They will use this information to develop new and improved therapies and therapeutic approaches. Individual projects are aimed at understanding the mode of action of existing front-line antituberculars, such as isoniazid and ethambutol, two drugs that form the backbone of modern short-course chemotherapy for TB. This knowledge is translated into screens for second-generation antituberculars based on the same basic mechanism of action.

DIR scientists are involved in a collaborative effort to understand the mode of action of a new series of compounds, called nitroimidazopyrans, which were developed by the PathoGenesis Corporation of Seattle, Washington. These drugs are the first new compounds that have been put forward for preclinical testing and evaluation against TB since the rifamycins were introduced in 1972. The compounds were shown to have significant activity against bacteria that are not actively replicating, a finding that has important implications for the one-third of the world's population that harbors latent bacilli and is at continued risk for the development of active TB.

NIAID's increased support for TB research has resulted in significant advances in our understanding of the basic biology, microbiology, and immunology of TB, which will result in the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.

# Emerging and Reemerging Infectious Diseases

New infectious diseases continue to "emerge." Within the past two decades, improved diagnostic and detection methods have revealed a number of previously unknown human pathogens. (For a list of emerging and reemerging diseases and pathogens, see the table below or www.niaid.nih.gov/dmid/eid/erd.htm.)

Largely as a result of better detection methods, evidence also is accumulating that infective agents play a role in diseases previously thought to be chronic and noncommunicable. In addition, changes in human demographics, behavior, and land use are all contributing to changing transmission dynamics by bringing people into closer and more frequent contact with pathogens. This situation may involve exposure to animal or arthropod carriers of disease. For example, transmissible spongiform encephalopathy (TSE) involves the transmission of disease from animals to humans through newly identified agents called prions.

In addition to the continual discovery of new human pathogens, old infectious disease enemies are "reemerging." Natural genetic variations, recombinations, and adaptations allow new strains of pathogens to appear. The immune system has not been previously exposed to these pathogens and therefore is not primed to recognize them (e.g., influenza and *Vibrio cholerae* 0139). Furthermore, human intervention plays a big role in reemergence. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistance, allowing many diseases to make a comeback (e.g., tuberculosis [TB], malaria, hospital-acquired infections, and foodborne infections).

## List of NIAID Emerging and Reemerging Diseases 2001

### Category I—Newly Recognized in the Past Two Decades

Acanthamebiasis
Australian bat *Lyssavirus*
*Babesia*, atypical
*Bartonella henselae*
*Cyclospora cayetanensis*
Ehrlichiosis
*Encephalitozoon cuniculi*
*Encephalitozoon hellem*
*Enterocytozoon bieneusi*
Hantaviruses
*Helicobacter pylori*
Hemorrhagic fevers, such as Rift Valley and Ebola virus
Hendra or equine morbilli virus
Hepatitis C
Hepatitis E
Human herpesvirus 8
Human herpesvirus 6
Lyme borreliosis
Microsporidia
Nipah virus
Parvovirus B19

### Category II—Drug Resistance

Drug resistance

### Category III—Reemerging Pathogens

Cholera
*E. coli* (EHEC, EPEC)
Enterovirus 71
Flaviviruses, such as dengue, West Nile virus, and yellow fever
Influenza
Prion diseases
Streptococcus, group A
*Coccidioides immitis*

The use of deadly pathogens, such as smallpox or anthrax, as agents of bioterrorism is an increasingly acknowledged threat to the civilian population. Moreover, many important infectious diseases have never been adequately controlled, on either the national or international level. Infectious diseases that have posed ongoing health problems in developing countries are reemerging in the United States, for example, foodborne and waterborne infections, dengue, and West Nile virus.

To enhance the capacity to deal with the challenges posed by emerging diseases, NIAID is constructing new biosafety-level-three (BSL-3) laboratories in Rockville and Bethesda, Maryland, and in Hamilton, Montana. These laboratories will give the Institute the capability to conduct BSL-3 animal studies and laboratory research on infectious agents, such as multi-drug-resistant *Mycobacterium tuberculosis* (Mtb). Research programs on pathogenic microorganisms, including *Borrelia, Yersinia*, the influenza virus, West Nile virus, and dengue virus, will be continued and expanded.

To an unprecedented extent, issues related to infectious diseases in the context of global health are on the agendas of world leaders, health policymakers, and philanthropies. This attention has been focused both on scientific challenges, such as vaccine development, and on the deleterious effects of infectious diseases on economic development and political stability.

Basic and clinical research is critical to the development of a national strategy to confront these microbial challenges. Such research increases our collective understanding of ever-changing microbial populations and permits this new knowledge to be transformed into better diagnostics, vaccines, and therapies. Basic research and research training also are the foundation for surveillance and response activities. In response to the threat of emerging and reemerging infectious diseases, NIAID has developed a strategy for addressing these issues through targeted research and training. That strategy, which was initially outlined in the Institute's 1996 document titled *A Research Agenda for Emerging Infectious Diseases* (www.niaid.nih.gov/publications/execsum/bookcover.htm), was updated in the recent NIAID strategic plan titled *NIAID: Planning for the 21st Century* (www.niaid.nih.gov/strategicplan/pdf/splan.pdf). In May 2001, NIAID released the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis* (www.niaid.nih.gov/publications/globalhealth/global.pdf). This document outlines the Institute's plans for the next decade for diagnosing, treating, and preventing these three infections and also lays out a plan for enhancing in-country research capacity.

The *Agenda* defines priorities in the following three broad areas:

- Expand the fundamental understanding of infectious agents, human susceptibility and immune responses to them, and the environmental factors that influence their emergence and spread;

- Strengthen the ability to develop and validate new tools to prevent and control infectious diseases; and

- Ensure that support for training and research is sufficient for building and

maintaining the scientific expertise and resources needed to meet future emerging disease threats.

During 2001, NIAID supported research initiatives on biodefense as well as on emerging and reemerging infectious diseases in multiple areas, including TB, Lyme disease, influenza, prion diseases, and other infectious diseases and deadly pathogens.

## Biodefense Research

NIAID continues to expand its research related to potential bioterrorism agents as part of a broad research agenda involving other agencies within the Department of Health and Human Services (DHHS) and the Department of Defense. NIAID's biodefense research program includes the following components:

- **Design and testing of diagnostics.** This component includes methods for rapid identification of natural and bioengineered microbes and methods for rapidly establishing a microbe's sensitivity to drug therapy.

- **Design, development, and clinical evaluation of therapies.** This component includes identification of several antimicrobial agents for each microbial threat pathogen, design of therapeutic drugs active against known drug-resistant variants, and development of broad-spectrum agents.

- **Design, development, and clinical evaluation of vaccines.** This component includes development of traditional and novel technologies, with an emphasis on safety and ease of administration, and development of new vaccines suitable for civilian populations of varying ages and health status.

- **Basic research on and infrastructure of genomics.** This component includes mechanisms of replication and pathogenesis, factors that play a decisive role in virulence and invasiveness, events or processes critical to initiating infection or influencing the severity of disease, generation of genome sequence information on potential bioterrorism agents, and enhancement of laboratory capabilities to handle potential bioterrorism agents.

See page 75 for more information on NIAID biodefense research.

## Emerging and Reemerging Infectious Diseases

### *Tuberculosis*

Mtb kills more people globally than any other single infectious agent. It is estimated that one-third of the world's population (more than 2 billion individuals) are infected with Mtb and that 1 in 10 of these individuals will develop TB during their lifetime. In 1999, an estimated 8.4 million persons developed TB, and 2 to 3 million patients died from this disease. The majority of TB cases occur in developing nations. Although TB is essentially a treatable disease, lack of availability of drugs in many countries and poor adherence to treatment schedules due to side effects and the long duration of treatment (6 to 12 months) have resulted in the development of single and multi-drug-resistant strains of Mtb that result in TB that is much more difficult to cure. Furthermore, the link between HIV and TB is

believed to be a major factor in the spread of TB. In 1997, of the 1.86 billion individuals worldwide who were infected with Mtb, approximately 10.7 million were also infected with HIV. In Africa, TB cases are increasing 10 percent each year due to HIV. These factors, combined with a suboptimal public health infrastructure in many countries, contribute to the ongoing spread and reemergence of TB worldwide.[9] For additional information on NIAID TB research, see page 62.

### *Lyme Disease*

Lyme disease (borreliosis) is the most prevalent tick-borne infectious disease in the United States. In the year 2000, 13,309 cases were reported throughout the United States to the Centers for Disease Control and Prevention (CDC). This number is an 18-percent decrease from the 16,273 cases reported in 1999. Decreases of 6 percent and 24 percent were reported in the New England States (4,361 versus 4,642) and in the mid-Atlantic States (6,770 versus 8,902), respectively.[10]

Data from two clinical trials that were analyzed in 2001 provide evidence that intensive antibiotic therapy is no more effective than placebo therapy in improving chronic Lyme disease symptoms. Study volunteers received standard antibiotic treatment for Lyme disease but suffered from persisting physical and cognitive problems related to their illness, including muscle or joint pain and memory and concentration problems often associated with fatigue. Researchers assigned volunteers at random to receive either antibiotic treatment or a placebo. The study compared treatment with 30 days of intravenous ceftriaxone followed by 60 days of oral doxycycline with treatment with intravenous placebo followed by oral placebo for the same duration. Researchers evaluated symptom improvement on the basis of patients' responses to a health-related quality-of-life questionnaire given 90 days after completion of the antibiotic or placebo regimen. Analysis of the responses showed no significant difference in the percentage of patients who believed their symptoms had improved, worsened, or stayed the same between the antibiotic treatment and the placebo group. Investigators also found that the impact of chronic Lyme disease on physical health was at least equal to the disability of patients with congestive heart failure or osteoarthritis. In addition, investigators found no evidence of the Lyme disease bacterium in the blood or spinal fluid of patients with chronic symptoms.[11]

These findings, coupled with the knowledge of treatment of other chronic infectious diseases caused by persistent bacteria, suggest that it is unlikely that a longer course of antibiotic therapy or different antibiotic combinations would further improve chronic symptoms. Therefore, patients can be spared a costly, ineffective treatment associated with side effects. Researchers will characterize the patients in the studies as thoroughly as possible to learn more about the mechanisms involved in chronic Lyme disease. The role that autoimmune reactions (immune system reactions against the body's own tissues) may play in persistent symptoms is also under investigation. Knowledge gained from these continuing studies could lead to more effective approaches for treatment of chronic Lyme disease.

In other NIAID-sponsored studies, researchers determined that in patients with chronic Lyme disease of at least 6 months duration, the most appropriate serologic test for prior infection with *Borrelia burgdorferi*, the spirochete that causes Lyme disease, is the IgG western blot assay. It is regarded by the CDC as the basis for determining that one is seropositive and thus has been exposed previously to *B. burgdorferi*. The present work shows that the testing of duplicate serum specimens from 21 patients with Lyme disease and 10 healthy controls, by a single reference laboratory using a commercially available IgG western blot kit, gave 100-percent concordant results for seropositive or seronegative reactivity, as well as highly reproducible results for the identification of individual bands. By contrast, Lyme urine antigen testing of 10 healthy control subjects gave contradictory results on samples from the same specimen in 8 of 10 cases and yielded consistently false-positive results in the other 2 cases. At least one sample of each specimen was falsely positive. These findings indicate that the Lyme urine antigen test (LUAT) is unreliable and should not be used for the laboratory diagnosis of active or suspected Lyme disease.[12]

NIAID DIR investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *Borrelia burgdorferi* in the early 1980s.[13] RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and relapsing fever microorganisms. Clinical investigators seek to better understand the natural history of chronic Lyme disease and possible causes for persisting symptoms. To this end, a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy is ongoing at the NIH Clinical Center.

### *Influenza*

In the United States, pneumonia and influenza are the sixth leading cause of death, responsible for 3.7 percent of all deaths.[14] Research supported by NIAID led to many new insights about how influenza causes disease. During 2001, NIAID-funded investigators discovered that a tiny change in one of the influenza virus's 10 genes is key to making certain strains of the virus especially virulent to humans. Dr. Yoshihiro Kawaoka and colleagues at the University of Wisconsin obtained samples of the H5N1 viruses that had infected Hong Kong residents during the 1997 outbreak. Testing these viruses in laboratory mice, the researchers found good correlation between how sick certain H5N1 strains made mice and how sick they had made humans. The researchers divided the H5N1 strains into two groups: those strains that caused systemic lethal infection in the mice were placed in one group, and those strains that were relatively benign were placed in a second group. Using reverse genetics, a technology that allows the specific switching of influenza virus genes, the investigators systematically swapped the genes from the harmful viruses and the benign viruses. The investigators then tested how those reengineered viruses affected mice. They discovered that the influenza PB2 gene—one of several genes involved in replication of the virus—gave the lethal virus its potency. Further testing of viruses that contained variations of the PB2 gene led the investigators to discover that a tiny molecular change

within the gene—a change of just one unit of RNA—appeared to be key to the virus's virulence. This discovery helps explain why the H5N1 influenza outbreak 4 years ago in Hong Kong killed an unusually high proportion of the people it infected. Furthermore, these results provide important information that may be useful in understanding the emergence of future viruses that may have pandemic potential.[15] For more information on Dr. Kawaoka's work in this field, other NIAID-supported influenza research, and background on the virus itself, visit *Focus on the Flu* at www.niaid.nih.gov/newsroom/focuson/flu00.

A second group of researchers determined that influenza enters and infects cells by a mechanism that involves the fusion of viral and host cell membranes. A peptide (protein fragment) on the surface of the virus facilitates the fusion process. NIH-supported researchers developed a system to determine the detailed structure of an influenza fusion peptide using an artificial membrane. Changes in pH induce fusion peptides to bend and penetrate deeply into the host cell membrane, thereby facilitating mixing of the virus and host cell membrane lipids and release of the viral genome into the host cell. Understanding the viral fusion process will allow researchers to more specifically target new antiviral therapies for influenza and other viruses that use membrane fusion as their means of infecting cells.[16]

Recent developments in influenza virus biology and molecular biology prompted the Division of Microbiology and Infectious Diseases (DMID) to organize a workshop on influenza virus reverse genetics. The workshop, held July 26 to 27, 2001, brought together an international group of researchers in influenza viruses as well as scientists outside of the influenza field with research experience in other human viruses, biosafety, and public policy. Discussions centered on using local biosafety committees to examine the research work that will be done at federally funded universities and to make risk assessments and safety recommendations. The need to reexamine the current biosafety guidelines in light of technical advances also was debated.

NIAID was notified on June 2, 2000, that lower-than-anticipated production yields for the 2000-2001 influenza A (H3N2) vaccine component and other manufacturing problems were expected to result in a substantial delay in the distribution of influenza vaccine and possibly substantially fewer total doses of vaccine for distribution than in the previous year. NIAID responded to this potential public health emergency by rapidly implementing a clinical trial at all five of DMID's Vaccine and Treatment Evaluation Units (VTEUs) and its Enteric Pathogens Research Unit (EPRU) to compare the immune response of a half-dose of flu vaccine with a whole dose of flu vaccine in healthy adults ages 18 to 49. The clinical sites enrolled 1,009 subjects in 11 days. Both the CDC and the Food and Drug Administration laboratories did the serology testing. Although the results of the study showed that the immune response generated by the half-dose was less than that of the full dose, the difference was less than expected and suggested that if a substantial shortage of vaccine had occurred in 2000, administration of a half-dose vaccine to healthy adults might have been an acceptable strategy.

In 1998, NIAID awarded a contract to Dr. Robert Webster, at St. Jude Children's Research Hospital in Memphis, Tennessee, for the surveillance and characterization of avian influenza viruses in the live bird markets in Hong Kong. Since that time, work done under this contract has provided invaluable information, including identification of the reemergence of the H5N1 viruses in Hong Kong in May of 2001, which resulted in the second mass slaughter of all live poultry. The contract also provides reagents (antibodies and recombinant influenza virus proteins) to researchers around the world and stores characterized influenza viruses suitable for possible use in human vaccine development.

NIAID continues to represent the NIH at interagency working group meetings convened by the National Vaccine Program Office to aid in the preparation of a U.S. National Influenza Pandemic Preparedness and Response Plan. Several sections of the Plan—including an overview and decision matrix—are currently under review by DHHS. NIAID has the lead in the development of the research agenda section of the Plan.

### *Prion Diseases*

Scientists in NIAID's Division of Intramural Research (DIR) are studying many emerging infectious diseases. For example, DIR has a productive and growing program focused on TSEs, or prion diseases. TSEs are fatal neurodegenerative diseases, such as scrapie, Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE or "mad cow" disease), and chronic wasting disease (CWD) of deer and elk. Since the BSE epidemic began in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In the fall of 2001, the emergence of BSE was reported in Asia when BSE-infected cattle were discovered in Japan.[17]

DIR TSE research is aimed at increasing our fundamental understanding of prion protein (PrP) and the mechanisms responsible for the accumulation of the abnormal form of prion protein (PrP-res) that appears to underlie TSE transmission and pathogenesis. Studies also are ongoing to clarify the mechanisms of cross-species transmission of PrP, work that is very important in light of the epidemiology of variant CJD, as well as the prevalence of CWD in deer and elk herds in the western United States. This work has provided new insights into the molecular basis of TSE species barriers and has uncovered evidence of a molecular barrier limiting susceptibility of humans, cattle, and sheep to CWD.[18] DIR scientists also have discovered compounds that show promise as potential TSE therapeutics.[19] One class of compounds that will be tested for efficacy against TSE disease in rodents holds special promise as a drug therapy for TSEs because the compounds can be absorbed from the drinking water and concentrated in the brain.[20] Studies of the potential use of antibody and other vaccine-based therapies for TSEs are ongoing in NIAID laboratories.

In FY 2001, NIAID also provided supplemental funding from the NIH Directors' Discretionary Fund for several activities related to TSEs, including the expansion of an ongoing contract for animal model evaluation

to include the evaluation of anti-TSE compounds, the establishment of containment capabilities for handling TSE materials, and the expansion of capabilities at CDC for collection of potential TSE-infected materials.

### *Other Infectious Diseases and Deadly Pathogens*

In FY 2001, with the cosponsorship of the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the NIH Office of Research on Women's Health, NIAID issued a request for applications titled "Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection" with the goal of encouraging research to develop or improve technologies to detect and validate the role of microbial pathogens in chronic diseases and cancer for which an infectious etiology is suspected (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-01-004.html). Awards are planned in FY 2002.

In addition, the Institute supports several unique international programs to promote scientific advances and cooperation on important infectious diseases and pathogens. These international programs include the following:

- **International Collaboration in Infectious Disease Research (ICIDR).** The ICIDR program is designed to promote collaborative research between U.S. investigators and scientists in 15 countries where tropical infections are endemic. The ICIDR program was recompeted in 1999 with a companion program from the Fogarty International Center (FIC) titled Actions for Building Capacity (ABC), which supports training of foreign investigators in the context of the ICIDR program. There are 14 NIAID-supported sites and four additional sites with support from the National Institute of Child Health and Human Development and the National Institute on Drug Abuse. There are nine ABC awards in the ICIDR program.

- **ICIDR Opportunity Pool.** The ICIDR Opportunity Pool was launched in the fall of 1999 to support emerging research opportunities due to unexpected disease outbreaks or scientific advances. To date, the ICIDR Opportunity Pool has supported research to evaluate the carriage of West Nile virus in birds migrating from the U.S. east coast to the Yucatan Peninsula, an investigation characterization of the Hantavirus outbreak in Panama, a project to evaluate genotypic and phenotypic correlation in *Cryptosporidium parvum* isolates from three different continents, and an investigation into the dengue outbreak in Bangladesh.

- **Tropical Disease Research Units (TDRU).** The TDRU program is a domestic grant award program intended to provide support for multiproject, interdisciplinary studies that seek to develop new strategies to control diseases caused by protozoa and worms.

- **Tropical Medicine Research Centers (TMRC).** The TMRC program provides support to four foreign institutions (currently located in Brazil, China, Columbia, and Mali) for research of direct relevance to the health of the people in tropical countries and promotes collaboration and exchange of information

between foreign and American scientists. This program is under a limited recompetition for FY 2002 funding.

- **International Centers for Tropical Disease Research (ICTDR).** Institutions supported by grants from the TDRU, ICIDR, and TMRC programs and other large international research sites, along with NIAID's DIR, make up the NIAID network of ICTDR. This program incorporates Institute-supported intramural and extramural tropical disease research centers into an interactive network focused on tropical infectious disease problems. The ICTDR held a special 10-year anniversary meeting of the ICTDR network in May 2001. The 11th Annual ICTDR meeting is scheduled for April 15-17, 2002.

- **U.S.-Japan Cooperative Medical Science Program (USJCMSP).** This program is a longstanding (36 years) bilateral cooperative research program involving U.S. and Japanese scientists who convene on a regular basis to address the public health priorities of Asia.

- **Vaccine Action Program (VAP).** The VAP, initiated in 1987, is a bilateral U.S.-India program that focuses on the development of safe and effective vaccines for major communicable diseases of interest to the two countries through joint research and development efforts. Currently, the focus of the program is on HIV/AIDS, malaria, and TB (www.niaid.nih.gov/dmid/other/indo).

- **International Training and Research in Emerging Infectious Diseases (ITREID).** In collaboration with NIAID, FIC funds a program to support international training and research in emerging infectious diseases. ITREID is now in its fifth year. The intent of this program is to enable NIH grant recipients to enhance laboratory, epidemiologic, clinical, and social science research and to train scientists and public health workers from developing countries and their U.S. counterparts in research, control, and prevention strategies.

- **International Cooperative Biodiversity Groups Program (ICBG).** NIAID continues to cosponsor the ICBG program, a project with a threefold mission—conservation of biodiversity, economic growth for developing countries, and discovery of pharmaceuticals from natural products. ICBG investigators have achieved extensive progress in identifying bioactive compounds from plants of Central and South America, Nigeria, Cameroon, Madagascar, Laos, and Vietnam. The ICBG program has become widely recognized as a model for research partnerships that acknowledge intellectual property ownership of indigenous communities.

## Scientists Find Hidden Piece of Influenza Virus*

For nearly 20 years, scientists have labored under the assumption that the influenza virus comprises only 10 protein molecules that form its structure and carry out its activities. However, scientists from NIAID's Division of Intramural Research have found a new, "hidden" influenza virus protein. This protein may kill immune system cells that fight the virus, thereby contributing to the virus's potency, the researchers say.

"We believe this is a groundbreaking finding, although we're not yet sure how deep the ground is," says Jonathan Yewdell, M.D., Ph.D., a viral immunologist who led the research team. "This might be the 'grand canyon' of the flu, in terms of understanding this virus's virulence, or perhaps only a narrow side ravine."

The scientists turned up this new protein by accident, while sifting through bits and pieces of "junk" peptides. Junk peptides are short protein molecules the virus creates once it infects a cell and begins replicating. They form when the process that translates viral genes into proteins goes awry, Dr. Yewdell explains. In other words, junk peptides result from genetic mistakes.

"We weren't looking for new proteins at all. We assumed the 10 known influenza proteins were all there were," Dr. Yewdell says. "We just wanted to know if immune system cells had learned to recognize any of these junk peptides. We thought that was an interesting question."

The immune system cells of mice, in fact, did recognize one of the peptides. When the scientists examined the gene encoding this peptide more closely, they noticed it was "suspiciously long" for mere junk. Wondering if this molecule might be a bona fide protein, Dr. Yewdell's team decided to see how much of it was created in cells infected with the flu virus. If it were junk, there should be only a few random copies of the peptide here and there. If it were a protein, large quantities of the molecule should be present. Dr. Yewdell used a technique called immunofluorescence, which makes the molecule glow green, to show how much of it infected cells contained.

"The cells we looked at just lit up," Dr. Yewdell says. "We saw large amounts of this molecule in the mitochondria of flu-infected cells, and we knew it was a real protein. It was one of those 'eureka' moments of discovery you live for in science. The junk turned out to be a jewel."

It turns out that this protein is created when ribosomes, the cellular machines that translate genes into proteins, begin reading the influenza gene called PB-1 in what was previously believed to be the wrong location. "One could say that lurking within the PB-1 gene is an overlapping gene that codes for this protein," explains Dr. Yewdell. "This alternate translation may have started out as a mistake, but the protein it produced was useful, so through evolution the gene was maintained and improved."

Tests showed the protein is toxic to human cells, especially immune system cells. "Next, we plan to learn more about the functions of this protein and how it accomplishes its tasks," Dr. Yewdell says. The team also wants to know whether this protein might have contributed to the virulence of the flu viruses that caused the Asian flu of 1957, the Hong Kong flu of 1968, and especially the Spanish flu of 1918, which killed 20 million people worldwide.

"Like many scientific discoveries, this one happened serendipitously, and it confirms the importance of supporting basic research on infectious diseases," concludes Anthony S. Fauci, M.D., NIAID Director. "When you have good researchers exploring interesting questions, they are bound to turn up crucial information."

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*Chen W et al. A novel influenza A virus mitochondrial protein that induces cell death. *Nat Med* 2001;7(12):1306-1312.

# Biodefense

Since 1982, when packages of Tylenol were contaminated with cyanide and the era of tamper-proof packaging dawned, the United States has recognized its vulnerability to chemical or biological terrorist attacks. The 1984 *Salmonella* contamination of salad bars by the Rajneesh cult to prevent Oregon voters from reaching the polls represents the first well-documented bioterrorist attack in the United States. However, it was the recent bombings of the World Trade Center and the Pentagon, the uncovering of advanced biological weapons programs in Iraq and the former Soviet Union, and the Aum Shinrikyo nerve gas attack on the Tokyo subway that focused concern on possible biological or chemical terrorist attacks against the United States.

Our ability to detect and counter bioterrorism depends to a large degree on the state of biomedical science. Biodefense research supported by NIAID emphasizes four areas: basic research, new diagnostic tools, vaccines, and new treatments or therapeutics.

## Basic Research

One of the most important basic research tools that has evolved in recent years is the ability to rapidly sequence the entire genomes of microbial pathogens, including potential agents of bioterrorism. This capability is important because when scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. In addition, because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins. Some agents, such as smallpox and other orthopoxviruses related to smallpox, have already been sequenced; the sequences of others, such as *Bacillus anthracis* (the anthrax bacterium) are in progress and close to completion. The fruits of this genomics research, coupled with other biochemical and microbiological information, are expected to facilitate the achievement of critical new goals, including the discovery of new targets for drugs and vaccines.

## New Diagnostic Tools

The NIH also supports research leading to the development of new and improved diagnostics. The goal of this research is to establish methods for the rapid, sensitive, and specific identification of natural and bioengineered microbes as well as the determination of the microbe's sensitivity to drug therapy. These scientific advances will allow health care workers to diagnose and treat patients more accurately and quickly.

## Vaccines

NIH-supported researchers are developing vaccines that are effective against many infectious agents, including those considered to be bioterrorism threats, with the intention of developing products that are safe and effective in civilian populations of varying ages and health status. Vaccines against pathogens are being developed using both traditional and novel technologies. Some novel technologies include the development of "DNA vaccines," various vector vaccines, and innovative systems for the rapid creation of vaccines against unfamiliar or genetically altered pathogens; these technologies are in various stages of development.

## New Treatments or Therapeutics

NIH therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be used by bioterrorists. Knowledge gained from basic and applied research is helping to identify additional targets for medications against agents of bioterrorism.

At the end of 2001, NIAID announced several new initiatives to accelerate research on bioterrorism-related pathogens and to help strengthen the nation's ability to deal with the public health threat posed by bioterrorism. These programs are designed to take advantage of the recent outpouring of ideas from academic and industrial scientists on ways to understand and combat potential agents of bioterrorism (www.niaid.nih.gov/dmid/bioterrorism).

Information on these new initiatives follows:

- **Anthrax Vaccine Contract**—seeks to accelerate development of new vaccines against the agent that causes this disease. NIAID has designated the Science Applications International Corporation (SAIC) to solicit and act as the main contact point for information about such potential vaccines. In particular, NIAID wants to support work on one of the most promising types of vaccines, a recombinant protective antigen vaccine.

- **Rapid Response Grant Program on Biodefense-Related Research**—will evaluate and fund new applications in 5 to 6 months after receipt, rather than the usual 9 or 10 months. This program will encourage researchers to investigate new prevention strategies for those at risk of exposure, new treatments for those infected, and improved diagnostics. It also will fund basic research that provides a better understanding of the disease-causing organisms, particularly information gleaned from the genomes of these organisms.

- **Partnerships for Novel Therapeutic, Diagnostic, and Vector-Control Strategies in Infectious Diseases**—will support work on new drug development and on faster, more accurate diagnostics for diseases of public health importance, including those caused by possible agents of bioterrorism. This program seeks to foster partnerships among government, academia, and the biotechnology and pharmaceutical industries. It builds on an established program that supports research on infectious diseases that are not a high priority for industry.

- **Exploratory/Developmental Grants: Technology Applications to NIAID-Funded Research**—will apply the latest genetic, imaging, and computer technology to currently funded research on infectious diseases, especially those caused by Category A agents of bioterrorism. With these grants, investigators can purchase new equipment or collaborate with researchers who already have the needed equipment and expertise. For example, this program might allow investigators to use the latest gene-knockout technology to better understand a particular infectious organism.

- **Small Business Program on Biodefense-Related Research**—is a one-time solicitation of applications for research on

agents of bioterrorism. This program is part of the already established small business grant program, but the administrative and review process will be streamlined.

- **United States-Based Collaboration in Emerging Viral and Prion Diseases**—is designed to establish multidisciplinary research units that will investigate viral and viral-like diseases. These units will quickly study threats from emerging and reemerging viruses and provide needed information about them.

- **NIAID Investigator-Initiated Small Research Grants**—will fund specific, well-defined projects that can be completed in 2 years or less. This program allows individual investigators to take advantage of unexpected research opportunities and to follow promising new leads.

NIAID also has a longstanding intramural research program aimed at shedding light on the mechanisms used by vaccinia and other poxviruses to regulate expression of their genes and replication of their genomes. This program has increased our understanding of poxviruses and facilitated the construction of improved vaccinia-expression vectors for vaccines and gene therapy. For example, NIAID intramural investigators have developed vaccinia-virus-expression vectors that express genes derived from a variety of sources, such as dengue virus, measles, and simian immunodeficiency virus, and are testing recombinant vaccinia viruses for use as live vaccines against infectious diseases. Proof-of-concept studies have shown that a replication-defective vaccinia virus, modified vaccinia virus Ankara (or MVA), containing respiratory syncytial virus (RSV) genes, primed and boosted immunity to RSV in primates.[21] Additional primate studies using an MVA-based measles vaccine confirmed the usefulness of this approach.[22] These findings indicate that MVA could be used as a vaccine to boost immunity in previously vaccinated or exposed persons.

NIAID intramural investigators have developed a system to study the fundamental biology of the interaction between *Yersinia pestis*—the bacterium that causes plague—and its flea vector to design strategies to interrupt transmission cycles. Scientists are using an artificial feeding apparatus to infect fleas with uniform doses of wild type or specific *Y. pestis* mutants to identify genes that are required for the bacteria to infect the flea midgut and to produce blockage of the flea foregut that is required for biological transmission. Intramural scientists also are establishing mouse and rat models of bubonic plague that incorporate the natural flea-borne route of transmission for studies of plague pathogenesis. The mouse model will be used to evaluate a new recombinant vaccine developed by the U.S. Army Medical Research Institute of Infectious Disease for its ability to protect mice against flea-borne transmission of *Y. pestis*.[23]

NIAID intramural scientists also are testing a new approach to developing a vaccine against tick-borne encephalitis viruses (TBEVs) that uses a chimeric virus—a virus composed of parts that are of different origin—composed of a highly attenuated live virus called Langat (LGT) and dengue virus type 4. This candidate vaccine was developed to provide resistance to the highly virulent, closely related TBEVs that share protective envelope epitopes with LGT. Significantly, the candidate vaccine

protected immunocompetent mice against the most virulent TBEV. Subsequent studies in rhesus monkeys suggest that the chimera is attenuated, immunogenic, and able to induce a protective immune response.[24]

Certain properties of the chimera, notably its attenuation for monkeys, its immunogenicity, and its failure to infect a highly permissive mosquito host, make it a promising vaccine candidate for use in immunization against severe disease caused by many tick-borne flaviviruses. This strategy also will be applied to construct chimeric viruses containing sequences from mosquito-borne West Nile flavivirus and the distantly related dengue type 4 virus to investigate the protective capacity of chimeric viruses against West Nile encephalitis.

NIAID investigators' studies of relapsing fever agents focus on two areas: (1) improving the serodiagnosis—or diagnosis by means of a reaction using blood serum or other serous fluids in the body—of relapsing fever by using recombinant DNA technology to clone genes of *Borrelia* spirochetes that express proteins that induce specific and detectable antibody responses and (2) examining how spirochetes adapt to their tick and mammalian hosts. Efforts toward improving serodiagnosis are directed at cloning and expressing the GlpQ gene, which encodes an enzyme of *Borrelia recurrentis*, the causative agent of louse-borne relapsing fever (LBRF). Testing for anti-GlpQ antibodies will allow serologic confirmation of LBRF and provide a means for retrospective serologic testing in areas endemic for LBRF. NIAID also began large-scale genomic-sequencing projects with *Borrelia hermsii* and *Borrelia turicatae*, which will ultimately allow the study of the differential expression of genes in ticks versus mammals. These approaches should help identify determinants associated with the pathogenicity of relapsing fever spirochetes.

## NIAID Responds: Extending the Smallpox Vaccine Supply

Smallpox virus (*Variola major*) is considered one of the most dangerous potential biological weapons because it is transmitted easily from person to person and few people carry full immunity to the virus. In addition to basic research of the virus, NIAID research on smallpox focuses on extending existing vaccine stocks to increase the number of available doses and developing new vaccines, treatments, and diagnostic tools to detect the disease quickly.

With smallpox eradicated, vaccinations against the disease have not been required in the United States for nearly 30 years.* Individuals who did receive a vaccination three decades ago are believed to have little immunity to the virus left, and people born in the United States since that time have not been vaccinated at all.

No new smallpox vaccine has been manufactured in almost 20 years.† Approximately 15 million doses of the traditionally used and highly effective smallpox Dryvax vaccine have been stored by the U.S. Government since production of the vaccine was stopped in 1983.‡ Until additional vaccine is produced, a bioterrorist attack involving smallpox would require the use of these existing smallpox vaccine stores to protect those at immediate risk.

In 2000, NIAID initiated a small pilot study to address concerns about the limited stock of smallpox vaccine. Conducted at St. Louis University Health Sciences Center, this study assessed the ability to "stretch" the current supply of vaccine by comparing several dilutions of Dryvax with undiluted vaccine. The results showed that the full-strength vaccine had maintained its potency. In addition, approximately 70 percent of people who received a 1:10 dilution of vaccine developed a sore followed by a scab at the injection site and antibodies in their blood, indicating an immune response.

Building on the earlier pilot and in response to increasing concerns regarding the threat of bioterrorism, NIAID accelerated the design and implementation of a larger multisite study to determine the feasibility of maximizing the smallpox vaccine supply by diluting the existing Dryvax vaccine. The study was designed to evaluate three different doses of vaccine: full strength, a 1:5 dilution, and a 1:10 dilution. Researchers assessed the ability of the various vaccine doses to stimulate a scab, or "take," at the injection site and produce antibodies in the blood. Participants who did not develop a scab in 7 to 9 days after vaccination were given a second vaccination with the same dose they received the first time to determine whether this "booster" vaccination would improve the participant's response to the vaccine.

The study was conducted at several NIAID Vaccine and Treatment Evaluation Units around the United States, including St. Louis University, Baylor College of Medicine, the University of Maryland, and the University of Rochester. Together, these sites were able to enroll 679 volunteers and perform vaccinations in less than 3 months.

From this study, researchers will learn which vaccine dose given in a single injection elicits the desirable response among the largest number of people and whether "boosters" can fortify the immune response in those who did not react to the first injection. Using this approach, the U.S. Government hopes to develop a strategy for effectively protecting the greatest number of people with the existing vaccine supply, thus guiding the use of the remaining stockpile of smallpox vaccine, if needed.

(Additional smallpox information is available in Henderson DA et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 1999;281(22):2127-2137. Review. PMID: 10367824 [PubMed—indexed for MEDLINE].)

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* Centers for Disease Control and Prevention (CDC). Vaccinia (smallpox) vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2001;50(RR10):1-25.

† CDC. Notice to readers: smallpox vaccine no longer available for civilians—United States. *MMWR* 1983;32:387.

‡ DHHS (press release). HHS awards $428 million contract to produce smallpox vaccine: Acambis/Baxter will produce 155 million doses by end of 2002. November 28, 2001. www.hhs.gov/news/press/2001pres/20011128.html.

# Antimicrobial Resistance

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial compounds—are an increasingly important public health concern. Antimicrobial resistance has become a significant public health problem because of overuse of antimicrobial drugs and failure to ensure proper diagnosis, drug use, and adherence to treatment. The most serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and urinary tract infections. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the need to use more and broader spectrum drugs to clear resistant infections, untreatable infections leading to increased morbidity and mortality, and an increase in selective pressure leading to the spread of resistant organisms.

This phenomenon is prevalent in developed countries and is also a challenge for developing areas of the world. Factors in the emergence of resistant malaria parasites, diarrheal pathogens, and sexually transmitted bacteria include incomplete or inadequate antimicrobial therapy, ineffective counterfeit drugs, and lack of access to health care. New prevention and treatment strategies are needed, as well as making effective use of the tools currently available for fighting resistant infectious diseases.

Hospitals are a critical component of the antimicrobial resistance problem. Many factors are believed to contribute to the emergence of drug resistance among nosocomial pathogens, including overuse of broad spectrum agents, increasing numbers of susceptible and immunocompromised patients, use of invasive procedures and devices, and the breakdown of infection- and disease-control practices. As a result, methicillin-resistant *Staphylococcus aureus* (MRSA) has increased to 53.5 percent and methicillin-resistant coagulase-negative staphylococci to 88.2 percent. Increasing reliance on vancomycin has led to the emergence of vancomycin-resistant enterococci (VRE), bacteria that infect wounds, the urinary tract, and other sites. VRE has increased to 24.7 percent in intensive care units (ICUs) in the United States.[25]

One of the most disturbing trends is the movement of multi-drug-resistant pathogens out of the hospital setting into the community. MRSA, long a problem in ICUs and nursing homes, is an emerging community-acquired pathogen among patients without histories of hospital stays or previous infections. Four recently reported cases of MRSA in children were community acquired, resulted in death, and show the potential severity of this phenomenon.[26]

*Streptococcus pneumoniae* (pneumococci) causes thousands of cases of meningitis and pneumonia and 7 million cases of ear infection in the United States each year, and multi-drug-resistant pneumococci are common and increasing. Overall, 24 percent of isolates causing invasive disease are resistant to penicillin, with averages as high as 35 percent in some States. Penicillin-resistant isolates also show resistance to other antimicrobial agents.[27]

An estimated 300 to 500 million people worldwide are newly infected with the parasites that cause malaria, and an estimated 1 million people die every year from this infection. Resistance to chloroquine, once

widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.[28]

The incidence of multi-drug-resistant tuberculosis (MDR-TB) has increased dramatically in the past decade and is currently present on five continents. Infection with TB in people also infected with HIV is occurring in several regions, in particular Africa and Asia, with negative impact on clinical outcome. Drug-resistant strains are as contagious as those that are susceptible to drugs and often reflect mismanagement of therapy. MDR-TB is more difficult and vastly more expensive to treat, and patients may remain infectious longer because of inadequate treatment.[29]

Diarrheal diseases cause almost 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae*, *Salmonella typhimurium*, and *Vibrio cholerae*, are emerging. Worldwide, shigella has progressively become resistant to most of the widely used inexpensive antibiotics. Multiple-resistant strains have occurred in Latin America, Central Africa, and Southeast Asia. *S. dysenteriae* type 1 is now uniformly resistant to almost all first-line agents.[30]

There is increasing evidence that the use of antimicrobials in food animals is associated with the emergence of resistance among *Salmonella* and *Campylobacter* isolated from the meat of animals.[31] In response to this threat, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance, as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports a number of clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these networks are the AIDS Clinical Trials Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Unit, and the newly established Bacteriology and Mycology Study Group, with one unit directed toward serious resistant bacterial infections.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. The new initiative titled Partnerships for Novel Therapeutics and Vector Control Strategies in Infectious Diseases is designed to encourage partnerships for the development of new drugs and diagnostics in areas that are not currently a high priority for industry but are likely to have a high impact on public health. An initiative designed to encourage development of innovative approaches to antimicrobial resistance is planned for fiscal year 2003.

NIAID cochairs an Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration; several other Government agencies also are represented on this task force. In January 2001, *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues* was published in the *Federal Register*. The action plan reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, which is based on input from constituents and stakeholders and will serve as a blueprint for specific coordinated Federal actions. The action plan is available online at CDC's antimicrobial resistance web site: www.cdc.gov/drugresistance. A companion piece on international issues is being developed by this interagency group.

NIAID also investigates antimicrobial resistance in its Division of Intramural Research (DIR) laboratories. DIR investigators are studying the molecular mechanisms underlying antimalarial and antitubercular drug resistance as well as resistance to a variety of other antibacterial and antiviral drugs. Intramural scientists and their collaborators discovered the gene responsible for chloroquine resistance and deciphered the evolution of drug resistance to a class of compounds used clinically in the developing world to treat tuberculosis. NIAID clinicians, in a collaborative study with colleagues from the National Cancer Institute, recently made an important finding that may help to prevent HIV drug resistance. They determined that the rate at which HIV disappears from the blood during the first week of drug therapy accurately predicts a drug regimen's long-term effectiveness in an individual. The current approach is to measure the amount of virus in the blood after 4 to 8 weeks of therapy. Earlier recognition of the efficacy of a drug regimen will allow doctors to remove patients from ineffective regimens sooner, thus decreasing the emergence of drug-resistant viral strains.[32]

NIAID intramural researchers also are studying the genetic variability of *S. aureus* bacteria and the emergence of drug-resistant *S. aureus* strains. Using genome-scale DNA microarrays and evolutionary analysis, they demonstrated that methicillin-resistant *S. aureus* strains evolved multiple independent times rather than from a single ancestral strain.[33] This finding resolves a longstanding controversy in *S. aureus* research and also suggests that strains of *S. aureus* may become dangerous more rapidly than previously thought. DIR scientists are now conducting studies to determine whether certain stains of *S. aureus* are more prone to the lateral gene transfers that may result in the acquisition of a resistance gene and therefore should be subject to greater vigilance.

# Hepatitis C

Hepatitis C is an emerging disease in the United States and worldwide. Before 1990, transfused patients were vulnerable to an unidentifiable liver disease agent(s) known only as non-A, non-B hepatitis. Cloned and sequenced more than a decade ago, hepatitis C virus (HCV) was identified as the cause of most of these chronic infections. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV remains the leading reason for liver transplants in this country. Rapid improvements in HCV diagnostics have occurred both in terms of antibody detection and the presence of the virus directly, making the supply of blood and blood products in the United States very safe. New infections continue at the rate of 30,000 new cases a year in the United States.

Today, injection drug users are at highest risk, yet transmission also occurs sexually (greatest with multiple partners), as well as through other mechanisms involving inadvertent exposure to contaminated blood. Estimates today indicate that HCV is carried by more than 170 million people worldwide, with 4 million in the United States alone.[34] Approximately 75 percent of those infected become chronic carriers, many of them unknowingly. They manifest no overt signs of liver morbidity for decades while their livers are undergoing active disease progression.[35]

NIAID has aggressively pursued the expansion of HCV research through its development of the Hepatitis C Framework for Progress. With the aid of participating Institutes and Centers, an NIH-wide framework was drafted that incorporates the different missions into a cohesive global plan. The final plan was reviewed by outside experts and has been approved by both the NIH Institute and Center Directors and the NIH Director. The following research goals were identified in the framework:

- Understanding transmission modes to develop effective intervention strategies;
- Understanding pathogenic mechanisms and disease progression to develop treatments;
- Characterizing hosts' immune responses to infection to develop vaccines and prophylactic measures as well as therapeutic measures;
- Defining viral replication and recovery with therapy as well as developing new therapeutic strategies;
- Investigating clinical manifestations to develop noninvasive methods to evaluate current disease state, to predict outcomes, and to prevent or reverse disease progression; and
- Defining effective prevention and intervention strategies to improve health.

The tools needed to develop these goals include tissue culture systems, small-animal models, and well-defined clinical cohorts.

Current therapies include various forms of interferon, an interferon-ribavirin combination, and long-lasting forms of interferon with and without ribavirin. Each iteration has improved response rate. Unfortunately, these drugs have a significantly lower success rate in patients infected with the viral genotype that predominates in the United States, as well as in African Americans.

Genotype refers to the genetic makeup of an organism or a virus. At least six distinct HCV genotypes have been identified, and genotype 1 is the most common genotype found in the United States. Studies suggest that African Americans with genotype 1 treated with interferon for HCV have a lower end-of-treatment response than Caucasians.[36] Therapeutic targets are being addressed, including inhibitors of viral components, such as the polymerase, protease, helicase, and internal ribosome entry site, and other viral enzymes critical for replication.

Vaccine development for HCV will require increased understanding of the protective immune response and of viral immune evasion tactics. These areas can best be studied in individuals with acute (early) infection.

In 2001, NIAID sponsored a workshop to identify the research tools needed to facilitate and expedite research on HCV and the diseases associated with it. Participants included laboratory and clinical scientists conducting research on various aspects of HCV, such as replication, immunology, natural history, disease progression, and development of therapies and vaccines. This year, one of the Hepatitis C Cooperative Research Centers (HC CRCs) began a clinical trial in HCV chronic carriers using pegylated interferon and ribavirin. Researchers are oversampling African Americans by enrolling 75 African Americans and 50 Caucasians. The trial is structured to provide more definitive evidence related to response rate differences because African Americans respond so poorly to the current standard of care. In addition to clinical outcome, the same CRC houses a multidisciplinary group of investigators who will conduct bench studies beyond the actual clinical study.

NIAID-funded investigators developed a cell line that replicates a subset of HCV proteins. They demonstrated that interferon α, the principal therapy for HCV, inhibits replication. This cell culture advance brings a robust system to the field not only for identifying and evaluating new antiviral therapies for HCV but also for future genetic and replication studies. The lack of such systems has hampered efforts to design better drugs to treat HCV.

In an effort to sort out the roles of CD4+ and CD8+ T cells in viral clearance, a team of NIAID-funded investigators examined these two immune system cells in patients with various outcomes to HCV infection. The functions and manifestations of these two T-cell types are different. For example, CD4+ T cells are known to produce T helper cells that can send the immune response in different directions. On the other hand, CD8+ T cells are cytotoxic, or destructive, lymphocytes that destroy infected cells. Researchers found that a broad, strong CD4+ T-cell response is maintained indefinitely after recovery from HCV infection. In contrast, a weak and narrow CD4+ T-cell response is seen in persistently infected HCV patients. Surprisingly, circulating CD8+ cells were almost undetectable in both recovered and chronic HCV patients. Moreover, CD8+ memory cells obtained from persistently infected HCV carriers could be stimulated to expand, whereas those cells from recovered individuals could not be. This is important as a means or target of interrupting chronicity and therefore disease progression once methods to "awaken" this subpopulation of dormant CD8+ T cells *in vivo* are discovered

for chronic patients. These differences also are important for recovery or persistence as outcomes of infection.

NIAID continues to provide partial support for the National Institute of Diabetes and Digestive and Kidney Diseases' HALT-C trial's ancillary studies. The trial is evaluating the impact of long-term therapy on disease progression, including virologic and immunologic responses and their association with recovery.

NIAID's Division of Intramural Research (DIR) scientists are conducting research on the mechanism that leads to the transition from asymptomatic infection to chronic infection and recovery in response to therapy. This work includes studies of the relative importance of the virus versus the host immune response in determining the outcome of infection. Scientists are using standardized amounts of a single genetic strain of HCV to study the natural history of chronic hepatitis C in chimpanzees by mapping the mutations that occur over time. Additional studies will focus on the types of genetic mutations that help HCV evade the immune system and on the types of antibodies produced during the early immune response. Understanding these phenomena will allow the development of new tools for hepatitis C treatment and prevention. This area of HCV research also is being carried out by NIAID extramural scientists, including studies at the HC CRCs.

In addition, NIAID intramural investigators are accelerating research to develop an HCV vaccine. A number of grantees are participating in the same type of research. To this end, they have prepared and standardized doses of HCV that can be used to test the effectiveness of candidate vaccines in the chimpanzee and have distributed this key reagent to the scientific community. Intramural scientists also have developed and tested candidate DNA vaccines for HCV in chimpanzees. In addition, they are evaluating vectored vaccines. Although these experimental vaccines did not prevent infection, they did modify the course of the infection.

Vaccine studies are hampered by the lack of a small-animal model or an *in vitro* system in which to study HCV and fine-tune possible vaccine formulations. To address both the lack of a small-animal model and the poor growth of wild-type HCV *in vitro* (cell culture), DIR researchers are genetically manipulating HCV to identify an infectious cDNA of HCV that can replicate *in vitro* and *in vivo*.

Full-length cDNA copies of HCV genomes constructed from replicons adapted to improve growth in cell culture are being tested for viability, both in cell culture and in chimpanzees. Success would be an important step in the development of both live and inactivated HCV vaccines.

Institute and multi-Institute-based HCV efforts and initiatives continue to be a high priority for NIAID.

# Vaccine Research and Development

Vaccines are a safe, effective, and efficient means of preventing morbidity and mortality from infectious diseases. NIAID is the center of vaccine research and development within the Department of Health and Human Services. The Institute's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nurtured comprehensive, collaborative vaccine efforts among scientists in government, industry, and academic institutions. In setting priorities for vaccine development, NIAID weighs the severity of disease and expected health benefits, considers the scientific and programmatic gaps and opportunities, and studies the feasibility, given the status of scientific knowledge about particular diseases and their causative agents.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) supports the discovery and development of safe and effective vaccines to prevent HIV infection and AIDS worldwide. Toward this end, DAIDS has a comprehensive portfolio of research grants and programs spanning basic vaccine research and preclinical testing of candidate HIV vaccines, through human clinical testing in the United States and internationally.

The Division of Microbiology and Infectious Diseases (DMID) also supports a full spectrum of vaccine research to (1) prevent infectious diseases, such as tuberculosis (TB), malaria, cytomegalovirus (CMV), group B streptococcus, and chlamydial infections; (2) serve fragile populations, such as infants, older people, and immunocompromised people; (3) evaluate novel vaccine approaches, such as oral, transcutaneous, and combination vaccines; and (4) improve upon existing vaccines.

Both DAIDS and DMID support large clinical networks and have vaccine production contracts that provide opportunities to develop and test vaccine concepts at early stages of development. Infrastructure for regulatory oversight, site monitoring, and data management round out the vaccine development process. In collaboration with the Fogarty International Center, both Divisions support site development and training in clinical trials.

Research supported by NIAID's Division of Allergy, Immunology and Transplantation (DAIT) is designed to apply the fundamental principles of immunology to the development of improved vaccines. NIAID's Division of Intramural Research (DIR) conducts a wide-ranging vaccine program. Extensive efforts are under way to develop vaccines to prevent diseases of worldwide importance, such as malaria, genital herpes, chlamydia, hepatitis E, Lyme disease, dengue fever, AIDS, and diseases caused by respiratory syncytial virus and parainfluenza viruses. The Institute's Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease, with the primary focus of research being the development of vaccines for AIDS.

## Division of Acquired Immunodeficiency Syndrome

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic. Although

educational and counseling efforts have had some success and remain essential, it has become evident that these prevention activities alone are not sufficient to contain the spread of disease. An HIV vaccine represents the best hope for controlling the HIV epidemic. Worldwide, an estimated 40 million people are infected with HIV, and last year alone, an estimated 5 million people were newly infected. HIV/AIDS continues to take its toll in the developing world. In 2001, AIDS killed 2.3 million African people. An estimated 28.1 million Africans now have the virus. This figure includes the estimated 3.4 million new HIV infections in sub-Saharan African in the past year. In Asia and the Pacific, an estimated 7.1 million people are now living with HIV/AIDS.[37]

The NIH has several significant resources devoted to the development of safe and effective HIV vaccines. The AIDS Vaccine Research Working Group (AVRWG), the VRC, and NIAID's comprehensive HIV vaccine research program are key to advancing HIV vaccine research. The AVRWG, chaired by Dr. David Baltimore, stimulates HIV vaccine research and assists the NIH in developing a comprehensive research program aimed at expediting the discovery and development of a safe and effective vaccine. Bringing together intramural scientists from across the NIH, the VRC advances multidisciplinary research from basic and clinical immunology and virology to vaccine design and production. This work complements the comprehensive extramural research activities of DAIDS.

DAIDS supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages of concept genesis and evaluation through the Innovation Grant Program, and basic vaccine research and design, including testing in animal models, mechanism-of-action studies, and studies of immune correlates through the HIV Research and Design Program. The Integrated Preclinical/Clinical AIDS Vaccine Development Program targets research at the preclinical-clinical interface of the vaccine research pipeline, and the New Technologies for HIV and HIV Vaccine-Related Research supports the use of novel and innovative technologies to detect and quantitate HIV, optimize measurement of immune response to HIV and candidate HIV vaccines, and evaluate and quantitate immune responses responsible for the efficacy of licensed vaccines for other infectious diseases.

To help expedite the development of promising HIV/AIDS vaccines, DAIDS also established several novel public-private partnerships under a program titled the HIV Vaccine Design and Development Teams (HVDDT). These "teams" tap the different skills and talents of private industry and academic research centers and are given financial incentives to move strong HIV/AIDS vaccine candidates out of the laboratory and into human testing. The HVDDT program responds to the need to increase public-private cooperation in developing vaccines against globally important diseases, such as AIDS, TB, and malaria, and encourages pharmaceutical companies to invest more in AIDS vaccine research by partially offsetting their financial risk. To date, these contracts have resulted in progress toward the development of several clade B (the most prevalent subtype of HIV in the Americas and Europe), clade C (the most prevalent subtype of HIV in Africa and Southeast Asia), and multiclade vaccine candidates.

The HIV Vaccine Trials Network (HVTN), a global HIV vaccine research network, was established in 2000 to foster the development of HIV vaccines through testing and evaluating candidate vaccines in clinical trials. The network has the capacity to conduct all phases of clinical research, from evaluating candidate vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. With 29 sites spanning 4 continents, the HVTN builds on the work that was conducted by the Division's U.S.-based AIDS Vaccine Evaluation Group (AVEG), which carried out early-stage testing of vaccine candidates, and the HIV Network for Prevention Trials (HIVNET), which conducted domestic and international trials of HIV vaccine and other prevention strategies. (See page 31 for a map showing the HVTN sites.)

To date, NIAID has supported more than 58 HIV vaccine trials, including 54 phase I trials and 4 phase II trials, involving well over 3,800 volunteers. A total of 30 candidate vaccines and 12 adjuvants (a substance that enhances the immune-stimulating properties of a vaccine) have been tested with 1 or more of 10 routes or methods of administration.

The use of a combination vaccine approach has been shown to be safe and immunogenic in volunteers at both low and high risk of HIV infection. Studies also have shown that this approach can stimulate cellular immunity, resulting in cytotoxic T lymphocytes (CTLs) that can kill infected cells and in the production of HIV-neutralizing antibodies that can stop HIV from infecting cells. As a result, the combination approach holds promise because it stimulates production of HIV-neutralizing antibodies and cellular immunity.

The HVTN is conducting two phase II trials to further evaluate the safety and immunogenicity of a combination vaccine approach. One trial, which is being conducted at 10 sites in the United States, is testing a canarypox vaccine (ALVAC 1452) in combination with a gp120 boost (AIDSVAX B/B). The canarypox-HIV vaccine is made up of a weakened canarypox virus that has been genetically altered to contain selected HIV genes. Neither vaccine can cause HIV infection. The second trial, which is being conducted in Brazil, Haiti, and Trinidad and Tobago, also is testing the use of ALVAC 1452, but in combination with a different gp120 product known as AIDSVAX MN.

Preclinically, the vaccine candidates and concepts evaluated over the past year include DNA vaccines, a stabilized HIV envelope protein, new viral vectors, and HIV regulatory proteins. DNA vaccines and viral vectors incorporate HIV genes to produce specific HIV proteins that then induce an immune response. More than a dozen candidate vaccines are now advancing toward clinical studies by NIH-funded scientists in academia and the private sector.

Among the more promising of the new vaccine candidates or concepts tested to date is an HIV DNA vaccine used in combination with a vaccine virus booster vaccine. This vaccine was shown to be capable of protecting rhesus monkeys from HIV/SIV disease.[38] (SIV is an HIV-like virus that infects nonhuman primates.) Another HIV DNA vaccine study also was found to prevent the onset of clinical AIDS in rhesus monkeys when used in combination with an adjuvant.[39] Both of these HIV DNA vaccine candidates are progressing toward phase I human trials.

Other preclinical research discovered that HIV regulatory proteins, Tat and Rev, might provide an effective way to fight off infection and will be explored further as possible targets for HIV vaccines.[40] Adjuvants also have been shown to play an important role in HIV vaccine development. One recent study found that although the adjuvant itself was not well tolerated, it enabled recipients to receive a lower dose of a vaccine and still achieve the same level of immune response as those who received a higher dose of gp120.[41]

Future vaccine research efforts will continue to explore the use of adjuvants, including cytokines, as well as other novel vaccine approaches, such as the use of alphavirus replicons (nonreplicating alpha viruses engineered to carry genes encoding HIV proteins), fowlpox, adenovirus, and novel peptides, among others.

## Division of Microbiology and Infectious Diseases

Because vaccines can provide a safe, effective, and efficient means to prevent illness, disability, and death from infectious diseases, research leading to new and improved vaccines is a high priority for DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve the health of the nation. Factors that influence priorities for vaccine research include the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, and recommendations made by the National Vaccine Advisory Committee and other advisory groups. DMID designs and implements a comprehensive research program to develop new or improved vaccines that will prevent or reduce the incidence of such infections in susceptible populations. Advances in the fields of microbiology, immunology, and biotechnology are applied to the development of new vaccines and to the improvement of existing vaccines through research support on the following:

- New vaccines against major diseases caused by respiratory syncytial virus (RSV), malaria, group A and group B streptococci, and other bacterial, parasitic, and fungal infections of both children and adults;
- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections, such as group B streptococcus, and congenital diseases caused by CMV infection, toxoplasmosis, syphilis, gonorrhea, and chlamydia infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori* and drug-resistant bacteria such as pneumococcus; and
- Novel technologies to enhance the effectiveness of vaccines, such as adjuvants, proteosomes, and plasmid DNA approaches.

Vaccines of high public health relevance, developed often in collaboration with industry, are tested for safety and efficacy in preclinical studies. If they remain promising, they may be evaluated in the DMID Vaccine Evaluation Network, which includes the Vaccine and Treatment Evaluation Units (VTEUs) and

other units at universities across the United States. New vaccine candidates continue to be developed, spurred on by advances in the basic sciences. These vaccine units are an integral part of NIAID vaccine research efforts and support carefully planned and designed clinical trials of novel bacterial, parasitic, and viral vaccines and other biologics in people of all ages and risk categories. Also of importance are the surveillance of pathogens that are of special interest to NIAID and the capacity to undertake focused research linked directly to vaccine biology and immunology.

In addition, the evaluation of vaccine safety is an integral component of the NIAID vaccine research program. Safety is evaluated in every vaccine clinical trial sponsored by NIAID. Study participants are monitored closely for any adverse effects of the vaccinations they receive. Specific safety issues, such as the use of novel cell substrates for vaccine development and the evaluation of combination vaccines, are explored through scientific consultation with other Federal agencies and in coordination with the National Vaccine Program Office (NVPO).

DMID also supports research on the development and more effective use of approaches to the following:

- Generating long-lasting protective immunity against various infectious agents;
- Favoring the development of mucosal immunity or the production of an antibody of a given isotype;
- Increasing the immunogenicity of candidate vaccines or favoring the expression of a cell-mediated cytotoxic immune response; and
- Simplifying immunization regimens to reduce the number of immunizations required for protection and the number of visits to health care facilities and associated costs.

With an integrated and comprehensive research program in infectious diseases, microbiology, and immunology, NIAID is prepared to lead research efforts on the development of safe and effective vaccines for the prevention of a variety of infectious diseases. Thus, DMID is recognized as an effective participant in U.S. national vaccine policy. In the United States, NIAID collaborates with other vaccine agencies, including the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration, on issues of vaccine research, vaccine safety, and national immunization strategies, coordinated through the NVPO.

Internationally, DMID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization (GAVI) and the Multilateral Initiative on Malaria (MIM). GAVI was established in 1999 as an alliance of global partners to replace the Children's Vaccine Initiative. This global alliance has the support and participation of international agencies (e.g., the World Health Organization, UNICEF, and the World Bank), as well as bilaterals, industry, nongovernment agencies, and foundations. The creation of the Global Alliance has been accompanied by significant financial commitments from the Bill and Melinda Gates Children's Vaccine Program. The mission of GAVI is to save children's lives and protect people's health through the widespread use of safe vaccines, in the belief that every child, regardless of place

of birth or socioeconomic status, should be protected against vaccine-preventable diseases of public health priority.

In May 2001, NIAID released the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis* (www.niaid.nih.gov/publications/globalhealth/global.pdf). This document outlines the Institute's plans for the next decade for diagnosing, treating, and preventing these three infections by building sustained research capability domestically and internationally and enhancing international partnerships. As part of this plan, DMID continues to expand research and collaboration efforts to advance the development of new vaccines for malaria and improved vaccines for TB.

NIAID, in collaboration with CDC, requested that IOM establish an independent expert committee to review hypotheses regarding the relationship between specific vaccines and alleged adverse events. In response, IOM created the Immunization Safety Review Committee in September 2000. This committee reviews the state of knowledge regarding a specific immunization safety concern and communicates its results to providers and the public. In 2001, the committee met to review three important vaccine safety issues: measles-mumps-rubella vaccine and autism, thimerosal-containing vaccines and neurodevelopmental disorders, and multiple immunizations and immune dysfunction. Within several months of each meeting, the committee publishes a report to disseminate its findings, including recommendations for any additional actions (e.g., research or surveillance) that are needed to better understand these safety issues.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. These applications include the following:

- Use of recombinant DNA technology for the production of defined immunogens, as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate immune response in selected host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce health care costs and the number of visits to health care facilities.

## Division of Allergy, Immunology and Transplantation

DAIT supports research on immunologic mechanisms and novel technologies applicable to vaccine design and development. The Division currently funds nearly 100 vaccine-related research projects that aim to increase our ability to rationally manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Projects include basic studies of innate immune receptors for pathogen molecules, antigen processing and

presentation, the development of antibody and cellular responses, and the elaboration of immunologic memory. Other topics more immediate to vaccine applications include the development of new adjuvants to enhance immunity, the design of approaches to induce protection in mucosal tissues, and the discovery of novel methods for more effective delivery of immunizing agents.

In FY 2000, DAIT established four new Vaccine Immunology Basic Research Centers that focus on the fundamental aspects of human protective immune mechanisms in infectious diseases. Through the Human Immunology Centers of Excellence Program, DAIT supports numerous mechanistic studies that will contribute to our basic understanding of human immunity and vaccine responses.

DAIT established the program on the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines and supports several projects within the program that focus on hepatitis C, TB, malaria, and HIV. Under this program, DAIT supports the HLA Ligand/Motif Online Database, a web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasite, and self-proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs. Support is provided under a NIAID contract with the University of Oklahoma. The web site address is http://hlaligand.ouhsc.edu.

An important new area of disease prevention focuses on the use of vaccination approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease exists, development appears to be feasible based on studies in animal models. Vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. Vaccines for autoimmune diseases will "turn off" a destructive immune response that is directed at the body's own tissues. NIAID, in collaboration with multiple NIH Institutes and the Juvenile Diabetes Research Foundation International, awarded five cooperative agreements in FY 2001 to focus on development of the knowledge necessary to rationally design and implement strategies to prevent autoimmune diseases, including type 1 diabetes.

NIAID, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development, supports the Diabetes Prevention Trial—Type 1, a multisite cooperative clinical trial to test the efficacy of low-dose, parenteral insulin and oral insulin to prevent type 1 diabetes in high- and intermediate-risk populations, respectively. This is the first large nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. The arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which is testing the effectiveness of oral insulin to prevent the development of disease, is continuing to enroll participants.

The NIAID Tetramer Facility produces MHC/peptide reagents for T-cell detection and has provided more than 750 tetramers to investigators worldwide. Reagents are provided for the study of T-cell responses

relevant to vaccine research and development for many diseases, including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at www.niaid.nih.gov/reposit/tetramer/index.html. The National Cancer Institute also provides funding for the Tetramer Facility.

## Division of Intramural Research

DIR supports vaccine research in a number of important disease areas. For example, a hepatitis A vaccine that was developed in one of the DIR laboratories has been licensed. Candidate vaccines for influenza, parainfluenza, and RSV are tested for safety, immunogenicity, genetic stability, and efficacy at the DIR-supported VTEUs. Each year about 10 candidate vaccines are evaluated at the Johns Hopkins University VTEU. DIR also has a substantial malaria vaccine development program, which is described in the Malaria section on page 59.

Dengue is an emerging mosquito-borne viral infection that causes an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of potentially fatal dengue hemorrhagic fever each year. A live attenuated vaccine is a vaccine whose biological activity has not been inactivated but whose ability to cause disease has been weakened. Recently, DIR scientists conducted phase I testing of a live attenuated dengue type 4 vaccine candidate derived using recombinant DNA technology and found it was safe and immunogenic in human volunteers. This vaccine candidate not only shows promise as a vaccine against type 4 dengue virus but serves as a basis for creating a vaccine that protects against all four types of dengue virus. Larger controlled studies are planned to further evaluate this vaccine candidate in humans.[42,43]

DIR scientists also made a breakthrough finding that brings us closer to a vaccine against leishmaniasis, a group of diseases with a broad range of clinical manifestations caused by parasites of the genus *Leishmania*. These diseases, which affect many millions of people worldwide, are transmitted by various species of the sandfly. DIR scientists determined that proteins in the saliva of the sandfly increase the efficiency of transmission of the *Leishmania* parasite, and they then demonstrated that a vaccine containing sandfly protein can protect mice from *Leishmania* infection. These results suggest that the sandfly salivary gland proteins may serve as viable candidates for a vaccine against *Leishmania*.[44]

Traditionally, identification of potential new vaccine candidates has been a slow and laborious process conducted one gene or protein at a time. However, genome sequencing and other high-throughput analytic techniques now provide far more rapid and efficient methods to identify parts of an infectious agent that can be studied for their suitability as potential human vaccines. These modern tools recently allowed DIR scientists to identify 11 new group A *Streptococcus* (GAS) molecules that are common to all strep strains studied from worldwide sources, including patients with diseases ranging from strep throat to necrotising fascitis ("flesh-eating" syndrome). The discovery of these previously uncharacterized molecules is an important first step toward examining their potential suitability as a human vaccine for control of infections caused by GAS. The

high-throughput strategies used in this study demonstrate that potential new vaccines can be identified very rapidly by whole-genome investigations.[45]

## Vaccine Research Center

The Dale and Betty Bumpers VRC is dedicated to improving global human health through the rigorous pursuit of effective vaccines for human diseases. Established by former President Bill Clinton as part of an initiative to develop an AIDS vaccine, the VRC is a unique venture within the NIH intramural research program. The role of the VRC is to stimulate multidisciplinary research and fill the gap between new basic concepts in immunology and initiation of clinical trials through the application of state-of-the-art methods to rational vaccine design. Late in the summer of 2000, construction of the VRC was completed, and newly recruited scientists began moving into their laboratories.

This year, the VRC initiated a clinical trial testing the first AIDS vaccine invented at the new facility. This HIV DNA vaccine contains the DNA blueprint for two pieces of HIV: "gag," which is HIV's core protein, and "pol," which includes three enzymes crucial for HIV replication. Once inside the body, the DNA in the vaccine instructs certain cells to make small amounts of these HIV proteins. Because the vaccine does not contain genetic material for the whole virus, it cannot cause HIV infection. The study will enroll 21 healthy men and women to determine whether the vaccine is safe and whether the body makes an immune response to these proteins.

The construction of the Vaccine Development Facility (VDF) is another high priority for the VRC. The VDF will manage production of multiple vaccine candidates originating from the VRC. To achieve this objective, the VDF will function in concert with the Vaccine Production Laboratory located at the Bethesda campus in transferring new vaccine technology for pilot-scale production of clinical trial material.

# Drug Research and Development

The development of therapies to treat infectious and immune-mediated diseases is a key component of NIAID's mission. Basic research serves as the foundation for drug development through scientific advances in microbiology and immunology. Advances in these areas help to identify potential targets for therapeutic agents and potential strategies for treating infectious and immune-mediated diseases. Through collaborations with industry, academia, and other Government agencies, NIAID has established research programs to facilitate drug development, including databases of chemical structures and chemicals that can be screened for potential use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trials networks to evaluate the safety and efficacy of drugs and therapeutic strategies.

## Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes substantial resources to the discovery and development of new therapeutics, attempting to focus resources on areas of promise that receive insufficient support elsewhere. A strong portfolio of basic research serves as the foundation for these activities.

Over the past 12 years, researchers have had success in their drug-discovery efforts on a relatively small number of viral targets: reverse transcriptase (RT), the enzyme that catalyzes the synthesis of viral deoxyribonucleic acid (DNA) from the ribonucleic acid (RNA) template present in the incoming, or infecting, virion, and protease (PR), the enzyme that effects HIV maturation by cleaving and processing viral precursor proteins to their mature form. There also has been a great deal of success in suppressing HIV and decreasing the incidence of opportunistic infections by combining treatment with several RT and PR inhibitors (known as highly active antiretroviral therapy, or HAART). Nonetheless, many problems have emerged with these regimens, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by HAART. Thus, there continues to be an urgent need for new therapeutic entities and approaches to expand the number and clinical benefit of currently approved therapies.

HIV therapeutics are discovered through a number of approaches beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle, immunopathogenic studies to further understand the nature of HIV-mediated immune deficiency, genetic studies to define genes responsible for control of transmission susceptibility and disease progression, and strategies to restore or reconstitute effective immune function. The approaches are the foundation for targeted drug discovery, pursued through investigator-initiated grants, Small Business Innovation Research (SBIR) grants, contracts, the Novel HIV Therapies: Integrated Preclinical/Clinical Development Program (IPCP), and the HIV Therapeutics: Targeting Research Gaps Program.

The IPCP supports the discovery, preclinical evaluation, development, and pilot clinical study of novel agents and strategies to suppress HIV replication, interfere with

disease progression, reconstitute or repair immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is discovered, development proceeds through additional *in vitro* testing. Additional information is obtained by evaluating the agent's activity against a range of HIV isolates, testing in animal models of HIV infection, when appropriate, assessing the toxicity in different cell lines and animal models, and conducting pharmacologic studies. If appropriate, the IPCP supports early clinical evaluation in human studies.

The HIV Therapeutics: Targeting Research Gaps Program supports applied studies in specific gap areas identified in HIV therapeutics, including (1) new delivery or formulation methods to enhance the clinical potential of anti-HIV drugs and (2) validating new viral and cellular targets for drug development. Studies funded through this program should generate preclinical proof of concept on the therapeutic feasibility of a specific target or approach and engage in applied preclinical studies that accelerate the entry of the target or approach into therapeutic research and the development pipeline.

Another important element of the DAIDS therapeutics discovery and development effort is the acquisition and dissemination of information on agents or strategies that show potential for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also conducts a program of surveillance by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff members use these databases to monitor compounds already under investigation and to identify additional entities to be pursued. Information from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS conducts clinical trials to examine its effectiveness in improving the quality and duration of life for HIV-infected individuals. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). These programs investigate therapeutic agents and novel treatment approaches, including studies to evaluate safety, dose, activity, efficacy, and optimal use. Together, they represent the largest AIDS clinical trials network in the United States and probably in the world.

## Division of Allergy, Immunology and Transplantation

The Division of Allergy, Immunology and Transplantation (DAIT) supports the research and development of drugs and biologics to treat and prevent immune-mediated diseases. Areas of research include therapeutic approaches to autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues, including bone marrow. DAIT established collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of

immunotherapeutic agents currently being evaluated in clinical trials. DAIT-supported researchers are investigating ways to transfer genes that encode the immunotherapeutic molecules into lymphocytes or mucosal membranes for delivery to the patient.

Several investigations are under way to evaluate new and potentially more effective therapies for asthma and allergic diseases, including multiple approaches to immunization and development of new agonist or antagonist medications. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to prevent and treat autoimmune diseases. These Centers encompass expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel diseases, and type 1 diabetes.

DAIT Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation are evaluating a variety of therapies to improve graft survival and to prevent acute and chronic graft rejection. New approaches and therapeutic agents under investigation include monoclonal antibodies in conjunction with standard immunosuppressive therapy, new immunosuppressive drugs to prevent and reverse chronic rejection, pretransplant induction therapies to decrease acute graft rejection and to prevent the onset of chronic rejection, and intravenous gamma globulin to reduce high levels of sensitization among some end-stage renal disease patients, thereby enabling them to become candidates for transplantation.

DAIT, with cosponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, continues to support the Immune Tolerance Network (ITN). The ITN is a unique international, multi-institutional consortium that brings together more than 70 researchers and clinical specialists from 40 institutions in 9 countries. The ITN works closely with academic investigators and industry to study new approaches to induce donor-specific immune tolerance. Network investigators are conducting clinical trials to test the ability of tolerogenic approaches to support long-term survival of transplanted kidneys and human islet cells to treat type 1 diabetes. Tolerogenic therapies disable only the immune cells that attack transplanted organs, letting other immune cells function normally. In addition, the ITN also will conduct clinical trials of new tolerance-inducing therapies in autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and asthma and allergic diseases.

## Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports research to facilitate the discovery and evaluation of new drugs for infectious diseases. This research is supported at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Current drug development efforts address a wide spectrum of infectious agents, including hepatitis, tuberculosis (TB), sexually transmitted diseases (STDs), malaria, fungal diseases, and pneumonia.

The drug research and development efforts of DMID reflect the Division's broad purview and accordingly encompass a diverse range of target organisms and treatment strategies. The activities support all stages of drug discovery and development, from the test tube to the bedside, and, especially for animal model and clinical research, involve close collaborations with colleagues from the pharmaceutical industry and the Food and Drug Administration (FDA).

DMID also supports more than 40 large-scale genome-sequencing projects; this information has the potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

### *Discovery and Preclinical Evaluation*

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against hepatitis B virus (HBV), influenza, respiratory syncytial virus (RSV), cytomegalovirus (CMV), West Nile virus, vaccinia, and other herpes and respiratory viruses. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts.

DMID supports investigators conducting basic and applied research on the discovery and design of antiviral agents. These projects have led to the design of new drugs for influenza, CMV, poxvirus, and hepatitis infections. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. Recent studies have included demonstration of the superiority of the combination of acyclovir and the herpes simplex virus-specific antibody over either agent alone as a therapy for the mouse equivalent of neonatal herpes, and the development of a hamster model of West Nile virus encephalitis that will provide an inexpensive, readily available means to test potential therapies. Other recent findings have identified several drugs with activity against members of the poxvirus family, which might be helpful in the event of a bioterrorist attack using smallpox.

Basic research on microbe replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites and of strategies to develop new agents based on this knowledge. For example, research projects on malaria include identification and characterization of unique parasite biochemical pathways that may serve as targets for drugs, determination of the mode of action of existing and potential drugs, and analysis of the mechanisms by which the parasite has become resistant to existing drugs.

An increasingly important contributor to the emergence of many infectious diseases, including pneumonia and TB, is the emergence of drug-resistant pathogens. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. This situation is becoming an increasingly important public health concern. In response, the Public Health Service, under the leadership of the NIH, the FDA, and the Centers for Disease Control and Prevention, has developed an antimicrobial resistance plan, which provides a blueprint for specific

coordinated Federal actions to address the emerging threat of antimicrobial resistance. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) production development. NIAID has the lead in the area of research. *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues* is available online at www.cdc.gov/drugresistance.

### *Clinical Studies*

DMID clinical research is supported either by individual grants or by contract-supported programs, such as the Collaborative Antiviral Study Group (CASG) and the Bacteriology and Mycology Study Group (BAMSG). The CASG is supported by a single award to the University of Alabama at Birmingham and by subcontracts to more than 100 collaborating sites. The CASG has recently established the safety and effectiveness of a new dose of the standard antiviral drug acyclovir, advancing the treatment of neonatal herpes virus infections. In addition, the CASG has demonstrated that an anti-CMV drug can decrease hearing loss in infants with symptomatic congenital ear infection. Currently, the CASG is evaluating new therapies for congenital CMV, herpes simplex encephalitis, and RSV infections. Studies of experimental therapies for HBV and hepatitic C virus (HCV) are in the planning stages.

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, has supported clinical trials examining antifungal therapy in the opportunistic and endemic mycoses since the first study done in the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two new contracts were awarded to comprise the BAMSG and the Bacteriology and Mycology Biostatistical Unit (BAMBU). This change expands the scope of work to include a new patient risk group to address resistance to antibacterial agents in a nosocomial setting and to provide for a separate biostatistical and operations unit.

A phase I study evaluating a new monoclonal antibody treatment in patients who have recovered from AIDS-associated cryptococcal meningitis is open to enrollment and will be completed under this MSG contract. Recent studies in the MSG also include phase III evaluations of new formulations of an established antifungal compound (e.g., Ambisome) as well as evaluations of newer antifungals (e.g., voriconazole) in patients at high risk for developing invasive fungal infection. Other DMID-supported research groups that conduct drug evaluations as a part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases Cooperative Research Centers, and the Sexually Transmitted Diseases Clinical Trials Unit. In 2000, NIAID launched a phase III efficacy trial, Azithromycin Versus Benzathine Penicillin for the Treatment of Early Syphilis, through its STD Clinical Trials Unit. This trial is currently open to enrollment in the United States and Madagascar. The purpose of this study is to determine whether azithromycin, a drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment. In addition, single-project grants and contracts also support therapeutic evaluations for a number of diseases.

### *Treatment-Related Research*

The first step toward appropriate treatment of an infectious disease is the availability of a sensitive and specific diagnostic reagent. DMID supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. For example, DMID supports the development and manufacture of rapid, inexpensive diagnostic tests for STDs. The Division also supports research focused on the development of topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent sexually transmitted infections.

In September 2000, NIAID convened, with industry, the Summit on Development of Infectious Disease Therapeutics, to discuss the state of development of new therapeutics for infectious diseases, including ways in which NIAID could better assist industry and academia in antimicrobial drug development for public health needs. On the basis of recommendations from this meeting, NIAID developed a new research initiative titled Partnerships for Novel Therapeutic, Diagnostic, and Vector Control Strategies in Infectious Diseases to support the development of drugs and diagnostics for human infectious diseases of public health importance and products for controlling insects and other organisms that transmit infectious agents. A key component of this initiative is the development of appropriate partnerships among government, academia, and the biotechnology, chemical, and pharmaceutical industries.

## Division of Intramural Research

Much of the research under way in NIAID's Division of Intramural Research (DIR) is aimed ultimately at the development of more effective therapies for infectious and immunologic diseases. The DIR's basic studies of the immune system, disease pathogenesis, and microorganism structure, replication, and transmission often reveal potential new therapeutic targets for treating immunologic and infectious diseases. In addition, new technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. For example,

- DIR scientists are studying the basic mechanisms underlying the effectiveness of current TB medications and integrating genomics and combinatorial chemistry to hone development of second-generation therapeutics based on the same mode of action.

- Studies of mast cells, which initiate and perpetuate allergic inflammation, are identifying key biologic steps in the control of mast cell number and function to identify new approaches, such as cytokine-based therapies, to treating allergic inflammatory diseases.

- DIR investigations of the pathogenesis of prion proteins have identified compounds that inhibit the formation of the abnormal prion protein that is associated with the transmissible spongiform encephalopathies, often fatal neurologic diseases affecting animals and humans. These compounds are being tested in rodent models.

- NIAID AIDS researchers have designed a new recombinant protein that inhibits HIV binding to the CD4 receptor. The new protein has been engineered to address the

shortcomings of an earlier viral entry inhibitor called soluble CD4, one of the first anti-HIV-1 therapeutics to be tested clinically, which failed to demonstrate clinical efficacy. The new protein appears to have the biochemical properties necessary for efficient inhibition of viral entry and will be tested soon in an animal model.

In addition to these examples of studies under way in the laboratories, DIR scientists are conducting more than 80 clinical research protocols at the Warren Grant Magnuson Clinical Center on the NIH campus. Many of these protocols are testing the efficacy of new drug therapies developed in DIR laboratories.

## A SMART Study

NIAID is planning a long-term study to address important questions about the most appropriate use of currently available antiviral drugs for the treatment of HIV/AIDS. The study, Strategies for Management of Anti-Retroviral Therapies, or SMART, will be conducted by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) over a 9-year period and will eventually involve 6,000 patients.

When the HIV/AIDS treatment guidelines were first developed in the mid-1990s, it was recommended that strong antiviral drugs be used soon after HIV infection was detected to suppress HIV as much as possible. In the short term, this approach has been successful and has resulted in sharp declines in death and disability in the United States and other developed countries. Nonetheless, treatment regimens with these powerful drugs are difficult to follow and are expensive; they can cause drug resistance and serious side effects after long-term use. Recognizing these serious consequences, updated versions of the treatment guidelines do not recommend initiating therapy as early as in the past.

The SMART study is designed to ultimately provide information that will help physicians and their patients make informed treatment decisions. The study will compare two distinct treatment approaches and will follow enrollees for an average of 7 years. The study will measure clinical events, such as progression to full-blown disease or to death, which take longer to appear.

In the first year of the study, investigators will enroll 1,000 HIV-infected people and randomly assign them to either a "go-slow" or a "hit-hard-early" treatment strategy. The "hit-hard-early" strategy will use antiviral drugs to suppress HIV levels to low or undetectable levels. Patients enrolled in the "go-slow" arm of the study will not receive antiviral drugs until their CD4+ T-cell counts drop below 250/$mm^3$, and then they will take the drugs only until their CD4+ T-cell counts rebound above 350.

To take advantage of the wealth of information predicted to come from such a large and lengthy trial, the SMART study also will incorporate several substudies. One substudy, which will examine treatment effects on the heart, is the first of its kind. Another substudy will examine whether and how treatment changes body fat distribution and bone density, which are significant side effects of highly active antiretroviral therapy (HAART), in enrollees in each group. For additional information about the study, visit www.smart-trial.org.

# Sexually Transmitted Diseases

Sexually transmitted diseases (STDs) are critical global and national health priorities because of the devastating impact they have on women and infants and their relationship with HIV/AIDS. In the United States, more than 65 million people are living with an incurable STD, and an estimated additional 15 million people become infected with at least one STD each year, approximately one-half of whom contract infections that will affect them for the rest of their lives.[46]

A number of conditions may occur later as a consequence of having STDs, including infertility, tubal pregnancy, cervical cancer, fetal wastage, low birthweight, congenital or perinatal infection, and other chronic conditions such as neurosyphilis. Moreover, substantial biological evidence demonstrates that the presence of other STDs increases the likelihood of both transmitting and acquiring HIV. Recent studies indicate that the more prevalent nonulcerative STDs (chlamydia infection, gonorrhea, bacterial vaginosis, and trichomoniasis) and ulcerative diseases (genital herpes, syphilis, and chancroid) increase the risk of HIV transmission by at least threefold to fivefold.[47]

NIAID supports research for more effective prevention and treatment approaches to control STDs. These approaches include (1) the development and licensure of vaccines, topical microbicides, and treatments for the microbes that cause STDs, (2) understanding the long-term health impact that sexually transmitted pathogens have in various populations, (3) stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens, and (4) developing better and more rapid diagnostics.

To carry out these activities, NIAID supports a broad STD research portfolio (www.niaid.nih.gov/dmid/stds) that addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STD Cooperative Research Centers (CRCs), which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. Another program, the STD Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STDs. The Topical Microbicides Program projects conduct basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of STDs and HIV/AIDS infection.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis*, *Treponema pallidum*, and *Ureaplasma urealyticum*. Recently, the genomic sequences of *Neisseria gonorrhoeae* and *Haemophilis ducreyi* were completed; the genomic sequencing of *Lactobacillus crispatus* (normal vaginal flora) is in progress. These genome sequences have provided new insights into the pathogenesis of their associated diseases and pave the way for new opportunities to develop diagnostics, drugs, vaccines, and microbicides.

In FY 2001, NIAID continued to support and encourage the development and evaluation of STD diagnostics designed for point-of-care use through the Small Business Innovation Research mechanism. NIAID also initiated a

double-blind, randomized clinical trial of oral metronidazole with *L. crispatus* CTV 05 or placebo intravaginal capsules for the treatment of bacterial vaginosis. Data analysis for safety and effectiveness end points is anticipated in early 2002. The STD Clinical Trials Unit will conduct a three-site clinical study determining the concordance of trichomoniasis between male and female partners; this study will include a microbicide acceptability questionnaire. Data from this study will provide STD prevalence, which will be relevant for future domestic microbicide efficacy trials.

## Topical Microbicides

NIAID continues to focus its prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, or films, known as topical microbicides, as a means of protecting against sexual transmission of HIV and other STDs.

Topical microbicides work by killing HIV or other sexually transmitted pathogens or by creating a barrier and blocking their ability to enter or bind with cells. Ideally, microbicides would be unnoticeable, fast-acting against HIV and a broad range of other sexually transmitted pathogens, inexpensive, safe for use at least one to two times daily, and easy to store. In addition, microbicides with and without contraceptive properties are needed so that women's reproductive decisions do not affect their risk for HIV/STD infection.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive effort is to support research and development that leads to the identification of safe and effective topical microbicides. Toward this end, the Institute supports six Topical Microbicide Program projects that focus on research and development to advance topical microbicides and recently initiated the Microbicide Preclinical Development Program. This new program, which is cosponsored by the National Institute of Child Health and Human Development (NICHD), supports the discovery and preclinical development of novel or underexplored HIV microbicides. To date, three awards have been made by NIAID, and three have been made by NICHD. In addition, the Integrated Preclinical/Clinical HIV Topical Microbicide Program has been jointly established by NIAID and NICHD to conduct translational research—taking promising concepts into early pilot clinical trials. It is anticipated that awards will be made in 2002.

This year, NIAID also sponsored the third Topical Microbicide Preclinical Workshop to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV. The workshop served to review the progress of the Topical Microbicide Program projects, to facilitate collaborations among scientists from different disciplines and among academic and private-sector participants, and to encourage interactions between Food and Drug Administration regulatory staff and commercial sponsors. The workshop included representatives from the public and private sector, industry, government, foundations, and community advocacy groups.

NIAID supports large-scale *in vitro* screening of potential HIV transmission-blocking agents

through a contract with Southern Research Institute—Frederick, Maryland. Potential microbicides from the private sector and from academic and governmental sources are tested in several different assays to determine their ability to block HIV transmission from infected T cells to cultures of cells lining the human cervix. In the past year, a new assay was developed to monitor the activity of potential microbicides in the conditions that mimic the vaginal environment. To date, more than 1,825 unique compounds have been examined in nearly 4,200 primary and secondary assays. The colorless or lightly colored compounds with a high therapeutic index are undergoing additional evaluation to assess their potential for development as topical microbicides, to determine whether they cause intravaginal irritation or other adverse effects in experimental animals, and to determine whether they remain stable in the vagina after delivery.

NIAID also has a contract with the University of Washington for microbicide research. During the past year, 11 candidate microbicides were evaluated for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in nonhuman primates. Having been found to be safe in this model, three of these candidates have been tested further for efficacy against chlamydial challenge in the same nonhuman primate model.

Several promising topical microbicide candidates are in various stages of testing. BufferGel is an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive sexually transmitted pathogens, such as HIV. It has been tested in clinical trials through NIAID's HIV Network for Prevention Trials, or HIVNET, to evaluate its safety and tolerability. The first trial was conducted in the United States and was followed by a study in India, Thailand, Zimbabwe, and Malawi. The results of these trials indicate that BufferGel is nontoxic and well tolerated. A phase III trial of a nonoxynol-9 (N-9) film in Cameroon, which enrolled 1,200 participants, found that N-9 has no effect on the transmission of HIV, gonorrhea, or chlamydia infections when provided as part of an overall HIV/STD prevention program. No additional studies of N-9 are being conducted because of safety concerns and the potential for increased risk of HIV infection reported in preliminary findings during the 13th International Conference on AIDS in Durban, South Africa, in July 2000.

A phase I study (HIVNET 020) of PRO 2000, a synthetic compound that works by inhibiting HIV entry, was completed recently. The study, which was initiated in 1999 in Rhode Island and Pennsylvania and in Durban and Johannesburg, South Africa, was conducted in sexually active women who were at low risk of HIV infection and in sexually abstinent asymptomatic HIV-infected women. The study, which assessed different strengths of PRO 2000 gel administered intravaginally once or twice a day for 14 consecutive days, found that the product was well tolerated in both groups of women with no serious side effects. All of the women indicated their willingness to use the product again if it were shown to protect against HIV infection. Differences in PRO 2000 concentration, frequency of use, and HIV status did not appear to be associated with differences in the prevalence of adverse events.

Since both PRO 2000 and BufferGel have been found to be safe and well tolerated, NIAID is planning a phase II/III study to further evaluate their safety, effectiveness, and potential use. The study will be conducted through the HIV Prevention Trials Network (HPTN). (The HPTN is a large clinical trials network, with both domestic and international sites, that was established to develop and evaluate nonvaccine HIV prevention strategies, including topical microbicides. Additional information on the HPTN is located in the AIDS section of Selected Scientific Areas of interest on page 56.) Additional studies will be conducted to evaluate both products for penile safety.

NIAID also is initiating two phase I studies of new products: 9-(2-phosphonylmethoxypropyl)-adenine (PMPA), which inhibits HIV replication, and cellulose sulfate, an HIV entry blocker. PMPA gel prevented the infection of female monkeys with simian immunodeficiency virus (SIV), a relative of HIV, when they were exposed to SIV in the vagina. The study of cellulose sulfate will be conducted in collaboration with the CONRAD Global Microbicide Project.

A particularly novel approach to developing new microbicides involves the use of the bacterial strain *L. crispatus*, which naturally colonizes the vaginas of many women. These bacteria produce chemicals that kill harmful microbes, including those that cause STDs, and have been shown to reduce women's risk of getting gonorrhea, HIV infection, and bacterial vaginosis, a type of vaginal inflammation. This past year, NIAID-funded researchers initiated a study of oral metronidazole with *L. crispatus* or a placebo to determine its safety and effectiveness in treating bacterial vaginosis, as noted above.

To further advance the field of topical microbicide research, NIAID will be holding a workshop to address the unique aspects and complexities of conducting clinical trials to ascertain the safety and effectiveness of microbicides in international settings. In addition, a strategic plan is being developed to detail long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials. A panel of experts will review the plan within the year.

# Asthma and Allergic Diseases

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Chronic allergic conditions can significantly decrease quality of life, patient well-being, employee productivity, and school performance and attendance. Annual health care costs are more than $10 billion. NIAID's goal in asthma and allergic diseases research is the development of more effective treatments, prevention strategies, and behavioral interventions.

An estimated 55 million Americans are reactive to at least one of eight selected allergens known to contribute to allergic illness.[48] These allergens include house dust, fungus spores, cat and dog dander, ragweed, oak, perennial ryegrass, and Bermuda grass. The prevalence of allergic rhinitis (hay fever) varies widely among different countries, from 2 to 40 percent.[49] Two separate estimates of prevalence in the United States are 9 percent[50] and 16 percent,[51] and the prevalence of allergic rhinitis has increased substantially over the past 15 years.[52]

Atopic dermatitis is one of the most common skin diseases, particularly in infants and children. The prevalence of atopic dermatitis varies widely in different countries, from 1 to 15 percent. The estimated prevalence of atopic dermatitis in the United States is 9 percent,[53] and prevalence appears to be increasing.[54]

Food allergy occurs in approximately 8 percent of children 6 years of age or younger and in approximately 1 to 2 percent of adults.[55] The prevalence of allergy to peanuts and tree nuts is estimated at 1 percent of the U.S. population.[56] These two foods are the leading cause of fatal and near-fatal food-allergic reactions. About 1,000 Americans per year have severe allergic reactions and/or anaphylaxis to food,[57] and about 100 Americans, usually children, die annually from food-induced anaphylaxis.[58] Food allergy is the most frequent single cause of emergency room visits for anaphylaxis and accounts for 33 percent of such emergency room visits.[59,60]

According to the Behavioral Risk Factor Surveillance System survey, an estimated 14.6 million adults in the United States had asthma in 2000, and the prevalence of asthma among adults was 7.2 percent.[61] In 1997, the National Health Interview Survey (NHIS) was redesigned to quantify active asthma among adults and children through diagnosis of asthma by a physician as well as an episode of asthma during the past year. Data from the NHIS indicate that approximately 10.8 million Americans had asthma in 1998, with an overall prevalence of 3.9 percent.[62] The economic costs of asthma continue to rise. In 1998, asthma accounted for an estimated $12.7 billion in expenditures, with $7.4 billion in direct medical expenditures and $5.3 billion in indirect costs.[63]

Asthma disproportionately affects children and minority populations, particularly African Americans. In 1998, asthma was more prevalent among African Americans (5 percent) than whites (3.9 percent), and this disparity was greater among children. Asthma was more prevalent among African-American children younger than 5 years of age than among white children of the same age (7.0 percent and 3.9 percent, respectively),[64] and this disparity was even greater for hospitalizations, emergency room visits, and deaths. African Americans were 3.4 times more likely than whites to be hospitalized for asthma. Emergency room visits for African

Americans (204 per 10,000) were much more common than for whites (58 per 10,000). In 1998, 5,438 people died from asthma, or 2 per 100,000. The death rate among African Americans (3.9 per 100,000) was more than twice that among Caucasians (1.8 per 100,000).[65]

The cause, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent major areas of emphasis for NIAID's Division of Allergy, Immunology and Transplantation (DAIT). NIAID vigorously pursues research on asthma and allergic diseases by fostering investigator-initiated projects and by supporting cooperative clinical studies, a national network of research centers, and demonstration and education research projects.

In the Inner-City Asthma Study (1996-2001), NIAID and the National Institute of Environmental Health Sciences (NIEHS) are evaluating the effectiveness of two interventions among children ages 5 to 11 with moderate to severe asthma. The physician feedback intervention provides primary care physicians with up-to-date information on recent asthma symptoms, medication, and health care utilization. The environmental intervention involves home-based education to reduce exposure to environmental triggers, including environmental tobacco smoke, cockroaches, house dust mites, molds, furry pets, and rodents. A total of 941 patients were recruited and evaluated for both the 1-year intervention period and an additional year of followup. A substudy, jointly funded by NIAID, NIEHS, and the U.S. Environmental Protection Agency, is evaluating the impact of fine particles and co-pollutants on respiratory morbidity. Data collection for these studies was completed in September 2001, and analysis is currently under way.

NIAID supports the Asthma and Allergic Diseases Research Centers, which are the cornerstone of the pathobiology component of the Institute's asthma and allergy research program, providing support for basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of these diseases. In response to the recommendations of an expert panel convened in February 2000, the program requirements were revised to emphasize studies in humans. Two of the centers are cofunded by NIEHS.

NIAID collaborated with the Centers for Disease Control and Prevention to launch a program to disseminate and implement the very successful asthma intervention developed by the NIAID National Cooperative Inner-City Asthma Study (NCICAS, 1991-1996). This educational and behavioral intervention, delivered by an asthma counselor, has been shown to reduce symptoms and hospitalizations in inner-city children with moderate to severe asthma. NIAID-funded investigators translated the NCICAS research intervention into a form that can be efficiently used in a variety of health care delivery settings, including health maintenance organizations, health departments, and community clinics. The 4-year program targets children living in inner cities and is being implemented through 23 inner-city health care organizations throughout the United States. More than 6,000 inner-city children with asthma will benefit from the effort.

Scientific advances over the past several decades have revolutionized our understanding of the human immune system and have contributed significantly to extraordinary improvements in the treatment of many immune-mediated diseases. As the primary NIH Institute for research in immunology, NIAID has been at the forefront of many of these advances, including discoveries leading to the characterization of asthma and allergic diseases as immunologic disorders. With an enhanced understanding of the role of immune dysfunction in the pathogenesis of asthma and allergic diseases, NIAID is uniquely positioned to apply fundamental knowledge to develop novel therapies and eventually to prevent disease onset.

An important NIAID intramural study is examining how allergen immunotherapy (allergy shots) works to reduce or prevent reactions to allergens such as pollen, dust, or cat dander. The efficacy of allergen immunotherapy in asthma is modest; however, it remains the only known disease-modifying therapy for allergic asthma. Certain T cells (types of white blood cells) called Th2 cells produce substances that generate allergies. Other T cells called Th1 cells produce substances that have opposite effects. This study will determine whether allergy shots change the immune response to allergens by reducing the number of Th2 cells or by changing them into Th1 cells. A better understanding of how allergy shots work may help scientists develop more effective allergy therapies.

# Autoimmune Diseases

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. These diseases are a significant cause of chronic morbidity, costing billions of dollars annually in health care expenses and lost productivity. Autoimmune diseases can be divided into two main groups: organ-specific and non-organ-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Non-organ-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage.

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease.

Congressional interest in autoimmune diseases was expressed in both House and Senate FY 1998 Appropriations Committee Reports, encouraging the establishment of an NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC was established in June 1998 under the direction of NIAID. Committee members include representatives of 17 NIH Institutes, Centers, and Offices, the Food and Drug Administration, the Department of Veterans Affairs, the Centers for Disease Control and Prevention, and private organizations that support research in this area. The ADCC facilitates maximum coordination among groups working in areas of complementary and shared interests. The first report of the ADCC, published in December 2000, provides further details on the individual initiatives, sponsors, and current and planned research on autoimmune diseases. The report is located at www.niaid.nih.gov/dait/pdf/adccrev.pdf.

As described in the Children's Health Act of 2000 (Public Law 106-310), in FY 2001, the ADCC began developing a strategic plan for research on the epidemiology and burden of disease; etiology and pathogenesis; diagnosis, treatment, and prevention; and training, education, and information dissemination. It is anticipated that this research plan will be presented to Congress in spring 2002.

DAIT supports several multicenter research programs on autoimmune diseases. The Autoimmunity Centers of Excellence (ACE) support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies. Clinical trials are under way for SLE, lupus nephritis, and multiple sclerosis. Protocols for clinical trials in type 1 diabetes are in development. In addition, several collaborations among ACE investigators will address the immune mechanisms underlying the agents used in these trials.

In FY 1999, DAIT established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in 4 clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. The ITN will perform clinical trials of promising tolerogenic approaches to prevent or treat multiple autoimmune diseases. These clinical trials include the following:

- The "Edmonton Protocol" is an experimental islet transplantation protocol for patients with hard-to-control diabetes. The initial study, conducted by the University of Alberta, resulted in insulin independence for 17 patients. The ITN trial will further assess the safety and efficacy of this treatment regimen and expand the capacity for islet preparation and clinical transplantation at 10 sites in the United States, Canada, and Europe. Results of this international, multicenter trial will establish the baseline success rate for islet transplantation and facilitate the development of new tolerogenic ITN-supported islet transplantation trials.

- In addition, the ITN is developing clinical trials involving multiple tolerance-induction approaches for multiple autoimmune diseases, including multiple sclerosis and type 1 diabetes. To date, six clinical trials have been approved for implementation, all of which will have integrated studies aimed at identifying the underlying immune mechanisms involved in disease progression and therapeutic effect. The ITN is cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF). More information on the ITN is available on its web site at www.immunetolerance.org.

In FY 2001, NIAID, with other NIH Institutes and the National Multiple Sclerosis Society, issued the request for applications titled "Sex-Based Differences in the Immune Response" to support basic and clinical research to identify, characterize, and define sex- and gender-based differences in the immune response.

An important new area of disease prevention focuses on the use of vaccine approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease currently exists, such a vaccine appears to be feasible on the basis of studies in animal models. Vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. In FY 2001, NIAID, with several other NIH Institutes and Offices, established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research for the development of new targets and approaches to prevent autoimmune disease and to evaluate novel approaches in pilot and clinical studies.

In collaboration with NIDDK and the National Institute of Child Health and Human Development, DAIT supports a multicenter clinical trial, the Diabetes Prevention Trial—Type 1, to test whether insulin administration can prevent or delay the onset of type 1 diabetes in at-risk individuals. This is the first large, nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. The arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with

low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which is testing the effectiveness of oral insulin to prevent the development of disease, is continuing to enroll participants. This trial is expected to be completed in 2004. In addition, DAIT, in collaboration with NIDDK and the JDRF, supports two Diabetes Centers of Excellence to stimulate multidisciplinary research in diabetes.

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, DAIT is developing clinical trials to evaluate the safety and efficacy of hematopoietic stem cell transplantation as a treatment for several severe autoimmune diseases, including multiple sclerosis, SLE, and scleroderma.

DAIT supports two genetics research resources. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least two individuals are afflicted by two or more autoimmune diseases. The data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. More information can be found at www.madgc.org. DAIT, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation, supports the North American Rheumatoid Arthritis Consortium (NARAC). The NARAC collects clinical data and genetic material from families with rheumatoid arthritis, which are made available to investigators to facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis. More information can be found at http://narac.patternrx.com.

In FY 2000, NIAID joined several NIH Institutes and Centers and the JDRF in supporting the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that collects and shares data on genes of the human leukocyte antigen (HLA) complex. The IHWG will study five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy.

In addition, DAIT supports a project within the IHWG to discover single nucleotide polymorphisms (SNPs) in type 1 diabetes-related genes. SNPs are naturally occurring genetic variations that may affect the amount or function of the gene product. Once SNPs are identified, researchers will be able to analyze patient populations for the presence of these variations. The SNPs will be available in a public database to facilitate the search for susceptibility genes in subjects with type 1 diabetes.

Although we have gained considerable understanding of the immune mechanisms that mediate tissue injury in autoimmune diseases, much remains to be learned about the causes of these diseases, underlying genetic susceptibility, the regulation of T-cell and autoantibody production, and the characterization of the cells and chemical mediators of inflammation. NIAID is committed to furthering our understanding of the immunopathogenesis of autoimmune diseases and to promoting the application of basic research to clinical investigations, which may result in the development of more effective therapeutic approaches and prevention strategies for these devastating diseases.

# Immune Tolerance

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated disorders, including autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and rejection of transplanted solid organs, tissues, and cells.

Tolerance-induction approaches seek to selectively block or prevent deleterious immune responses. For example, in transplantation, donor-specific immune tolerance—a selective blockade of immune responses directed against the graft—would enable long-term graft survival without the complications and risks of global immunosuppressive therapy (e.g., infection, malignancy, and atherosclerosis). In asthma and allergic diseases, the goals of tolerance research are to develop methods to block immune responses, especially allergic (IgE) responses, to those allergens, such as cockroach and house dust mite, that cause or exacerbate these diseases. In autoimmune diseases, tolerance-induction approaches seek to block those immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Two decades of highly intensive and productive basic research in immunology have provided a solid foundation of knowledge and understanding that will enable the application of promising tolerance-induction strategies to the treatment of human disease.

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports basic research to elucidate mechanisms responsible for immune tolerance, translational research to facilitate the application of immune tolerance to human diseases, and clinical research of novel therapeutic approaches to induce and maintain immune tolerance in humans. New approaches are being sought to achieve the following:

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve currently suboptimal treatment protocols for immune-mediated diseases, such as the use of systemic immunosuppressive drugs in transplantation;
- Discover methods to prevent or reverse immune-mediated human disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

In FY 1999, DAIT established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in 4 clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. Trials under way or in development include the following:

- The "Edmonton Protocol," an experimental islet transplantation protocol for patients with hard-to-control type 1 diabetes.

- A trial to evaluate combined bone marrow and kidney transplantation for patients with renal failure caused by complications of multiple myeloma. The Massachusetts General Hospital has successfully treated two patients using this regimen, including complete withdrawal of all antirejection drugs. The ITN is supporting a multicenter trial of this protocol to further assess its efficacy and is conducting important scientific studies to understand the mechanisms of tolerance induction using this regimen. As with all ITN-supported clinical trials, this study will integrate research to identify the underlying immune mechanisms involved in disease progression and therapeutic effect.

- Studies to analyze the immune responses of liver and kidney transplant recipients who have maintained their transplanted organs for many years, despite discontinuation of antirejection therapy. Investigators will explore the immune mechanisms responsible for long-term antirejection, drug-free graft survival and will determine whether these patients have developed immune tolerance to their transplanted organs.

- Clinical trials involving multiple tolerance-induction approaches for several autoimmune diseases, including multiple sclerosis and type 1 diabetes. The ITN also is pursuing clinical trials involving multiple tolerance-induction approaches for asthma and allergic diseases and currently supports a trial of DNA-ragweed allergen conjugates for the treatment of allergic rhinitis. More information on the ITN is available on its web site at http://www.immunetolerance.org.

As clinical therapies for inducing tolerance are advanced, it becomes essential to develop procedures to monitor patient progress and provide physicians with tools for assessing the ongoing ability to maintain a tolerogenic state. These mechanistic assays are termed "tolerance assays." The ITN has established a set of core laboratories to develop diagnostic assays for the induction, maintenance, and loss of tolerance. These core facilities include microarray analyses of gene expression, bioinformatics to develop appropriate analytic tools for clinical and scientific data sets developed from the ITN-sponsored clinical trials, ELISPOT analyses of protein expression, and cellular assays for T-cell reactivity.

DAIT and the National Institute on Diabetes and Digestive and Kidney Diseases issued a request for applications to support the Non-human Primate Immune Tolerance Cooperative Study Group. This group was established in FY 1999 to evaluate the safety and efficacy of tolerogenic regimens in large-animal models of kidney and pancreatic islet transplantation. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplant recipients.

Other DAIT-supported research programs, which include studies on immune tolerance, are the Autoimmunity Centers of Excellence, the Human Immunology Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance.

# Transplantation

Illnesses such as end-stage renal disease, diabetes, liver disease, coronary heart disease, lung disease, and leukemia affect millions of Americans. For many of these patients, transplantation of solid organs, tissues, or cells can avert, and in some cases reverse, the severe outcomes of these diseases. Transplantation procedures have increased 81 percent from 1988 to 2000,[66] providing relief to tens of thousands of patients. Advances in transplantation also have increased the likelihood of graft acceptance by the recipient's immune system. Today, transplantation procedures are performed using more than 25 different organs and tissues, with the 1- and 5-year graft survival rates approaching 94 percent and 78 percent, respectively.[67] Despite these successes, two major impediments remain: immune-mediated graft rejection and the critical shortage of donor organs.

## Immune-Mediated Graft Rejection

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad spectrum of research on immune-mediated graft rejection, including basic research in transplantation immunology, preclinical evaluation of new therapies, and clinical trials of promising therapies to improve short- and long-term graft survival. The major goals of DAIT-supported research in transplantation are to (1) understand the processes and mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells, (2) develop preclinical models to evaluate clinically applicable therapies to prevent and treat rejection and prolong graft survival, (3) evaluate promising new agents and approaches in clinical trials to improve graft survival and function, and (4) accelerate research in immune tolerance to grafts to reduce or eliminate the need for lifelong immunosuppressive drugs.

Kidney transplantation accounts for 58 percent of all solid-organ transplants and is the preferred therapy for end-stage renal disease.[68] To establish and coordinate multicenter clinical trials of new immunosuppressive protocols in kidney transplantation, DAIT established the Cooperative Clinical Trials in Adult Kidney Transplantation (CCTAT) in FY 1991. This program, renewed in FY 1995, includes 38 transplant centers throughout the United States. Among a number of important accomplishments, CCTAT trials have changed the standard of care for kidney transplant recipients. In FY 1994, DAIT established the Cooperative Clinical Trials in Pediatric Kidney Transplantation (CCTPT). Renewed in FY 1999, CCTPT develops clinical strategies to treat and prevent graft rejection in children and to address the unique characteristics of the pediatric immune system. Clinical trials within CCTPT are examining the causes of lower patient and graft survival rates in children versus adults and the effects of immunosuppressive drug therapy on growth retardation.

DAIT established program projects in transplantation immunology to enhance understanding of the processes involved in controlling the immune response and to apply this knowledge in the clinical setting to prolong graft survival. The goals of this research program are to identify and characterize molecules, cells, and mechanisms involved in graft rejection and to develop therapeutic regimens that facilitate successful transplantation by modulating the immune

response. Projects include basic investigations on the genetics and regulation of the immune system and clinical research that defines immune factors affecting the success of transplantation.

Despite substantial improvements in short-term graft survival, long-term graft survival remains poor, primarily because of chronic rejection. Although chronic rejection presents a fairly uniform clinical picture, little is known about its etiology, including the factors that determine onset and severity, the targets of immune reactivity, and what controls the degree of variability in the rejection process between patients. These gaps in knowledge hinder the development of surrogate markers of chronic rejection and new treatment and prevention approaches. In FY 2001, DAIT and the National Heart, Lung, and Blood Institute collaborated on a new request for applications titled "The Immunopathogenesis of Chronic Graft Rejection," with five awards made in FY 2001. This new research initiative will enhance our understanding of the immunologic mechanisms that underlie chronic rejection of solid organs, improve diagnostic criteria to predict rejection, and identify novel approaches for clinical intervention.

In collaboration with the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK), DAIT supports the Non-human Primate Immune Tolerance Cooperative Study Group to develop novel approaches to tolerance induction. This group was established in FY 1999 to evaluate the safety and efficacy of tolerogenic regimens in large-animal models of kidney and pancreatic islet transplantation. In islet transplantation, the insulin-producing islets are separated from the whole pancreas before transplantation. Researchers hope that islet transplantation will allow people with type 1 diabetes to live without daily injections of insulin. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplantation in nonhuman primates.

Improvements in immunosuppressive therapy have dramatically reduced acute rejection and have increased the 1- and 5-year graft survival rate for all organ transplants. However, many serious side effects are associated with the use of globally immunosuppressive drugs to prevent graft rejection. Reducing these risks while improving graft survival is a priority in transplantation immunology. One promising alternative to immunosuppression is to interrupt or modify the immune response to establish specific tolerance to the graft. In FY 1999, DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators from 40 institutions in 9 countries, to test promising treatment regimens in 4 clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. The first clinical trial conducted by the ITN is based on the "Edmonton Protocol,"[69] an experimental islet transplantation regimen for patients with hard-to-control type 1 diabetes. The initial study, conducted by the University of Alberta, resulted in long-term insulin independence for 17 patients. The ITN trial will further assess the safety and efficacy of this treatment regimen and expand the capacity for islet cell preparations at 10 sites in the United States, Canada, and Western Europe. Results of this

international, multicenter trial will establish the baseline success rate for islet transplantation and facilitate the development of new tolerogenic ITN islet transplant trials. (More information about the ITN is available at the following web site: www.immune tolerance.org.)

NIAID is supporting a pilot study of kidney transplantation in HIV-positive patients. The current antiviral therapy available to HIV-positive patients has significantly increased their life expectancy. However, a complication of this therapy is kidney toxicity, leading to end-stage renal disease. With increased life expectancy, these patients can be candidates for kidney transplantation. The objectives of this study are to determine the safety and efficacy of kidney grafts into HIV-positive patients and the interactions between the antirejection and the antiviral therapies. Ten transplant centers in the United States will participate in this study, which will be conducted through the CCTAT.

DAIT will support a clinical trial of immunomodulatory dietary supplements in kidney transplant recipients. An earlier clinical trial suggested that the addition of arginine and omega-3 fatty acids to the diets of kidney transplant recipients may reduce the incidence of posttransplant infections and reduce both hospital stays and the frequency of acute rejection episodes. The clinical trial will attempt to reproduce the results of the earlier trial, measuring additional relevant clinical parameters, including effects on blood pressure and cholesterol and triglyceride levels.

In FY 2001, NIAID, with cosponsorship from several NIH Institutes and the JDRF, continued its support of the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that collects and shares data on histocompatibility genes. Histocompatibility genes allow the immune system to respond to specific pathogens, but these genes also play a role in the unwanted immune responses that occur in graft rejection and autoimmune diseases. The IHWG seeks to standardize and improve histocompatibility testing worldwide through the discovery, development, and distribution of information about new tissue-typing methodologies and reagents. These efforts will help to ensure that transplant recipients receive the best-matched donor organs available. In addition, the IHWG will focus on (1) expanding knowledge of the role of histocompatibility genes in cancer and autoimmune diseases and (2) furthering the understanding of human leukocyte antigen (HLA) diversity in ethnically distinct populations to improve donor matching and graft survival. For more than 20 years, DAIT has supported efforts to identify and characterize antigens of the major histocompatibility complex (MHC), which are critical in matching organ donors and recipients. Until recently, knowledge about the differences in the type and frequency of transplant antigens in minority populations has been limited. This lack of knowledge has been a major factor in the relatively poor outcomes of minority transplant recipients compared with Caucasians and has contributed to the lower number of transplants

performed in minority populations. In addition, further analysis of HLA gene diversity in the Alaskan Yupik Eskimo population is being conducted by the IHWG's diversity/anthropology component.

DAIT support of a national program to identify and characterize MHC antigens in African Americans, Hispanics, and Native Americans has contributed to the development of improved methodologies for tissue typing, thus improving donor and recipient matching. These efforts also have led to advances in the technology used for tissue typing, significantly decreasing the time necessary to perform these procedures and to transplant an organ.

## Donor Organ Shortage

In 2000, 22,908 organ transplants were performed in the United States, including 13,332 kidneys, 4,950 livers, 2,197 hearts, 956 lungs, 436 pancreata, 910 kidney-pancreas combinations, 79 intestines, and 48 heart-lung combinations.[70] Despite the success of transplantation programs in this country, there remains a critical shortage of donated organs. The ever-increasing waiting list for transplants has risen to more than 79,000 patients.[71] In 2000, 5,742 of those patients died while awaiting a transplant.[72] In an effort to address these issues, DAIT supports research to increase donation through donor registries, which are used to identify potential donors, and through the development and testing of educational interventions in selected populations. DAIT also sponsors studies of alternatives to living and cadaveric donation. Xenotransplantation, the use of nonhuman organs, tissues, or cells in human transplantation, has been largely unsuccessful because of vigorous immune-mediated rejection. DAIT-supported research in xenotransplantation focuses on better understanding the human immune response to antigens present on the surface of organs or tissues from nonhuman species and the development of methods to allow rapid identification and treatment of infectious diseases that might occur by transmission of disease-causing organisms across species barriers.

With each advance in transplantation immunology comes a new set of challenges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without global, lifelong immunosuppressive drugs, and increasing the supply of donor organs.

# Minority and Women's Health

The Office of Special Populations and Research Training (OSPRT) oversees the Institute's activities in the area of minority and women's health. In FY 2001, OSPRT was involved in the development of the *NIAID Strategic Plan for Addressing Health Disparities*. This plan focused on three goals: (1) to conduct research to identify and address health disparities among various populations affected by infectious and immunologic diseases, (2) to increase the number of minority scientists and grantees, and (3) to improve education and outreach activities for the transfer of health information to these populations. The plan is available online at the following NIAID web site as an Adobe document: www.niaid.nih.gov /healthdisparities/niaid_hd_plan_final.pdf.

For more than 50 years, NIAID has contributed to progress in understanding, treating, and preventing infectious and immunologic diseases known to occur disparately in minority populations. As outlined in its recent strategic plan on health disparities, NIAID continues to prioritize (1) basic, clinical, and epidemiologic research on these health problems, (2) efforts to increase participation of minority scientists in its research, and (3) outreach activities designed to communicate research developments to these groups.

## Minority Health Activities

### *Asthma and Allergic Diseases*

Chronic allergic conditions pose serious threats to quality of life, patient well-being, employee productivity, and school performance and attendance. The cost to the health care system is more than $10 billion annually. Over the past 15 years, asthma morbidity and mortality have increased in the United States, particularly among poor African-American inner-city residents. Asthma is more prevalent among minority children, and members of minority groups are three times more likely to die from this disease. Low socioeconomic status, exposure to cockroach allergens and pollutants, lack of access to medical care, and lack of self-management skills all contribute to increased morbidity from asthma.

The Inner-City Asthma Study (1996-2001), cofounded by NIAID's Division of Allergy, Immunology and Transplantation (DAIT) and the National Institute of Environmental Health Sciences, is a multicenter, randomized, controlled trial testing the effectiveness of two interventions to reduce asthma morbidity and severity among inner-city children ages 5 to 11 with moderate to severe asthma. In this 950-patient study, the baseline data show unanticipated and very high rates of sensitization to a range of indoor allergens. Preliminary data highlight many serious obstacles to allergen remediation in inner-city environments. DAIT also supports a demonstration and education research program on asthma in medically underserved, predominantly inner-city Hispanic and African-American populations. Many of the components of this program are carried out through NIAID's Asthma and Allergic Diseases Research Centers. For example, one project uses home visits by nurses for self-management training and environmental interventions in high-risk infants with wheezing. Another demonstration and education project developed a unique computer-based medical and self-management

training program for families of children with asthma.

### *Autoimmune Diseases*

Collectively, autoimmune diseases afflict an estimated 5 percent of the U.S. population. Several autoimmune diseases disproportionately affect minority populations. For example, systemic lupus erythmatosus (SLE) is more common and more severe in African-American women and is also two times more prevalent among African-American men than among Caucasian men. Reports indicate an increased prevalence of SLE and rheumatoid arthritis among many Native American tribes, and scleroderma is found to be more prevalent in African-American women. Because of their chronic nature and debilitating complications, autoimmune diseases exact high medical and socioeconomic costs.

To address the health disparities caused by autoimmune diseases, DAIT supports the Autoimmunity Centers of Excellence, a program that integrates basic and clinical research, including pilot clinical trials of promising immunomodulatory and tolerance-induction strategies. In addition, DAIT established the Multiple Autoimmune Diseases Genetics Consortium in FY 1999, a repository of genetic and clinical data and materials collected from family members who have two or more distinct autoimmune diseases. DAIT also has collaborated with other NIH Institutes and Centers to stimulate research in several specific areas of autoimmune disease with health disparities implications. The Division is funding an epidemiologic study to investigate the prevalence of SLE in women in Africa and the Caribbean and in African-American women in the United States. The findings from this study will address the genetic and environmental factors important in the pathogenesis of this autoimmune disease.

### *Organ Transplantation*

NIAID research in transplantation focuses on immune-mediated graft rejection and the shortage of donor organs. Major research programs include the Cooperative Clinical Trials in Adult Kidney Transplantation; the Cooperative Clinical Trials in Pediatric Kidney Transplantation; support of a national program to identify and characterize major histocompatibility complex (MHC) antigens in African Americans, Hispanics, and Native Americans to improve donor matching and clinical outcomes; the International Histocompatibility Working Group, which has access to large patient cohorts of diverse ethnic and geographic origins and will provide tremendous statistical power for population-based studies of human leukocyte antigen (HLA) genetics in human diversity, transplantation, autoimmune diseases, and immune responses to pathogens; and Immunopathogenesis of Chronic Rejection in the Immune Response to increase understanding of the immunologic mechanisms that underlie chronic rejection of solid organ grafts, improve diagnostic criteria, and identify novel approaches for clinical intervention.

### *Primary Immunodeficiency Diseases*

Primary immunodeficiency diseases may be frequently underdiagnosed, especially in minority populations in which prevalence estimates appear to be disproportionately low

compared with Caucasians. Although these racial differences may have an underlying genetic basis, preliminary data suggest that primary immunodeficiency diseases are not recognized in U.S. minority populations. Lack of access to consistent health care may contribute to underdiagnosis in these populations. In FY 2000, NIAID provided support for a new research project to test the hypothesis that primary immunodeficiency diseases are not recognized in minorities. Using an urban hospital setting with a large Hispanic and African-American patient population, the project is testing a new method for identification of patients with these diseases. Culturally sensitive educational materials also are being developed for training of minority health care providers.

### *Immune Tolerance*

In FY 1999, NIAID, with the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Foundation International, established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in 4 clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. The clinical research program will evaluate new tolerance-induction strategies to treat asthma and multiple autoimmune diseases, including diseases such as SLE, which disproportionately afflict minority women.

### *Hepatitis C*

Hepatitis C virus (HCV) infection is the most common chronic bloodborne viral infection in the United States. Various surveys indicate that HCV disproportionately affects minority populations; moreover, available treatments for HCV tend to be less effective for African Americans than other populations.[73]

NIAID currently funds 45 HCV grants and 6 Hepatitis C Cooperative Research Centers (HC CRCs). The HC CRCs make up a research consortium whose goals are to identify components of HCV and the body's immune response, as well as individual genetic factors that have a crucial impact on recovery from initial and chronic infection, disease progression and severity, and the influence of cofactors that impact HCV disease.

### *Tuberculosis*

During 2000, approximately 78 percent of active tuberculosis (TB) cases were reported among racial and ethnic minorities.[74] The problems of urban poverty, high HIV infection rates, and the effects of household crowding may contribute to the disproportionate impact of TB on minorities.

Over the past decade, dramatic increases in NIAID funding for TB research have allowed the Institute to support a wide range of TB initiatives and an expanded community of TB researchers. NIAID's extramural TB research program supports more than 135 grants for basic and applied TB research, including awards to support the genomic sequencing of *Mycobacterium tuberculosis* and other strains of the bacterium that cause TB. NIAID recently recompeted the Tuberculosis Research Unit at Case Western Reserve University, which is conducting clinical trials of potential TB therapeutic, preventive, and diagnostic strategies.

One of NIAID's high priorities is the development of improved TB vaccines, as outlined in the Institute's *Blueprint for Tuberculosis Vaccine Development*. Through the TB research materials and vaccine testing contract, NIAID provides TB research reagents to qualified investigators throughout the world. The Institute also plans to fund an initiative designed to revitalize research on the mechanisms underlying latent *M. tuberculosis* infection.

### *Sexually Transmitted Diseases*

Sexually transmitted diseases (STDs) are critical global and national health priorities because of their devastating impact on women and infants and their causal association with HIV infection. Reported rates of some STDs, such as gonorrhea and syphilis, are as much as 30 times higher for African Americans than for whites. This disparity is due to many factors, including differences in the distribution of poverty, health-seeking behaviors, and access to quality health care.[75]

NIAID supports research for more effective prevention and treatment approaches to control STDs. The Institute's ongoing efforts include the STD Cooperative Research Centers, the STD Clinical Trials Unit, and the Topical Microbicides Program projects. In addition, NIAID continues to initiate and support a variety of other research projects that focus on (1) developing vaccines, topical microbicides, and treatments for the microbes that cause STDs, (2) developing better and more rapid diagnostics, (3) sequencing the genomes of sexually transmitted pathogens, and (4) understanding the long-term health impact of sexually transmitted pathogens in various populations.

### *Acquired Immunodeficiency Syndrome*

AIDS continues to affect minorities disproportionately. In absolute numbers, African Americans have outnumbered whites in new AIDS diagnoses and deaths since 1998. Of the new AIDS cases reported in 2000, 47 percent were among African Americans, 19 percent among Hispanics, 32 percent among whites, 0.5 percent among American Indian/Alaska Natives, and 0.9 percent among Asian/Pacific Islanders. Among women, African Americans and Hispanics account for 77.5 percent of all AIDS cases; among men, African Americans and Hispanics account for 51.5 percent of all cases. Minority children are also disproportionately affected.[76]

One of the greatest challenges facing AIDS researchers today is the recruitment and retention of minority patients for clinical trials. As the epidemic expands in minority communities, inclusion of these patients in clinical trials is particularly urgent to ensure that the results of research are applicable to all populations affected by the disease. An additional challenge is the recruitment of underrepresented minority investigators to AIDS and AIDS-related clinical and basic research disciplines. Consequently, NIAID supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing and treating HIV disease in minority communities, training minority investigators, and fostering infrastructure development.

NIAID directs a large national clinical trials program consisting of three groups: the Adult AIDS Clinical Trials Group, the Terry Beirn Community Programs for Clinical Research on AIDS, and the Pediatric AIDS Clinical Trials Group. Each of these groups strives to ensure

enrollment of a sufficient proportion of minority subjects.

NIAID's epidemiologic research explores the clinical course and factors contributing to transmission of HIV infection in a variety of populations. Groups of inner-city women and their children are the focus of the Women and Infants Transmission Study (WITS) and the Women's Interagency HIV Study. Both WITS and the Multicenter AIDS Cohort Study, a prospective longitudinal study of HIV disease in homosexual and bisexual men, are studying access to medical care among people of minority backgrounds.

The HIV Vaccine Trials Network (HVTN) is dedicated to developing an HIV vaccine through testing and evaluating candidate vaccines in clinical trials. HVTN also will initiate community outreach programs to educate people about HIV and vaccine research and to encourage participation in clinical trials. Through this outreach initiative, HVTN hopes to enroll a diversified population in its clinical trials, with an emphasis on recruiting minorities and women. Educating the community about HIV clinical trials also is an important part of outreach for the HIV Prevention Trials Network, which is exploring nonvaccine prevention strategies to reduce HIV transmission at U.S. and international sites.

## Women's Health Activities

A significant number of infectious diseases within NIAID's scientific mission have a major, and often disproportionate, impact on women's health. This list includes immune-related diseases, HIV/AIDS, chronic fatigue syndrome (CFS), and STDs.

### *Autoimmune Diseases*

Many autoimmune diseases, such as SLE and scleroderma, disproportionately affect women. These diseases affect women in their most productive years, and the impact of the diseases on families and society can be substantial. To further understand the differences in the immune responses between males and females, DAIT and other NIH Institutes and Offices issued an initiative titled Sex-Based Differences in the Immune Response to support multidisciplinary research to identify, characterize, and define sex-based differences regulated by hormonal and nonhormonal mechanisms in response to exogenous antigens, the innate and adaptive immune response, and systemic and mucosal immunity. In collaboration with several other NIH Institutes and Offices, DAIT also established Autoimmunity Centers of Excellence to support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies. The Centers are enrolling participants in clinical trials of SLE, lupus nephritis, and multiple sclerosis.

### *Acquired Immunodeficiency Syndrome*

AIDS is now the fifth leading cause of death for all women ages 25 to 44 and the third leading cause of death for African-American women in this age group. Women now comprise approximately 17 percent of the total number of adults and adolescents with AIDS. The World Health Organization estimates that more than 80 percent of adult HIV infections worldwide are due to heterosexual transmission.[77]

AIDS affects minority women at a disproportionately high rate. African Americans and Hispanics constitute 77 percent of AIDS cases among women. AIDS cases among African Americans are more than two times greater than those among Hispanics and eight times greater than the rate for whites. However, among African-American women, injection drug use accounts for 44 percent of all AIDS cases reported since the epidemic began, with 37 percent due to heterosexual contact.[78]

Mother-to-infant transmission of HIV—which can occur during pregnancy or childbirth or through breastfeeding—accounts for more than 90 percent of all cases of childhood HIV infection worldwide. An estimated 1,800 HIV-infected babies are born each day in the developing world. Fortunately, recent studies supported by NIAID indicate progress in this area. The latest findings stem from the continued followup of breastfeeding mothers and their babies enrolled in a clinical trial (HIVNET012) and indicate that a new drug regimen using nevirapine could prevent a large number of these infections in babies.[79]

Women suffer from many of the same complications of AIDS that afflict men as well as gender-specific manifestations, such as recurrent vaginal yeast infections, pelvic inflammatory disease (PID), genital ulcer disease, severe herpes infections, gender-specific abnormalities related to infection with human papillomavirus, and carcinomas of the vulva and vagina.

Several NIAID-funded clinical research networks—including the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Beirn Community Programs for Clinical Research on AIDS—are examining various treatment regimens for AIDS/HIV. In addition, NIAID intramural scientists conduct clinical studies at the NIH Clinical Center. All these clinical trial networks identify and evaluate different strategies for treating women and their infants and for preventing perinatal transmission.

### *Chronic Fatigue Syndrome*

Patients with CFS can suffer for years from debilitating fatigue, muscle and joint aches, tender lymph glands, and a host of other symptoms, including problems with mental concentration and memory. CFS is diagnosed two to four times more often in women than in men, and its onset may follow infection, stress, or trauma related to irregularities in the immune system, the nervous system, or the endocrine system.[80]

In 2000, NIAID and the Department of Health and Human Services CFS Coordinating Committee held state-of-the-science workshops to evaluate the current state of CFS research and to identify promising new areas for scientific exploration. Areas addressed at these meetings included sleep disorders, neuroendocrinology, pain, cognitive disturbance, neurally mediated hypotension, immunology, and functional disability. NIAID and the National Institute of Nursing Research are cosponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients. The Institute continues to support three CFS Cooperative Research Centers, which conduct broadly focused research addressing basic science and clinical and epidemiologic aspects of CFS, including its causes, characteristics, and treatment.

### *Sexually Transmitted Diseases*

An estimated 15 million new cases of STDs occur in the United States each year, with approximately one-fourth of these new infections affecting teenagers. Although some STDs (e.g., syphilis) have declined to all-time lows, others (e.g., genital herpes, gonorrhea, and chlamydia) continue to spread through the population, posing a significant public health problem. Symptoms of STD infection in women are minor or nonspecific, particularly in the early stages. As a result, STDs in women sometimes are not diagnosed until late in the disease, with possible adverse health effects, such as poor pregnancy outcome. Furthermore, STDs that occur during pregnancy also can negatively affect the fetus or newborn.[81]

The consequences of STDs are often devastating. For example, untreated chlamydia and gonorrheal infections can lead to PID, which often results in scarring of a woman's fallopian tubes and life-threatening tubal pregnancies. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can cause complications of pregnancy, such as fetal wastage, low birthweight, and congenital infection.

The control of many STDs has been complicated by the frequency of asymptomatic infections; the lack of safe, effective vaccines; the cost and technical difficulty of available diagnostic tests; the expense of single-dose oral therapies; and the absence of effective methods that women can use to protect themselves from STDs. NIAID has addressed these challenges with a multidisciplinary research strategy that includes basic science, vaccine development, behavioral science, development of topical microbicides (chemical and physical barriers that women can use intravaginally to inactivate sexually transmitted pathogens), and development of rapid and inexpensive diagnostic tests.

As research has increasingly connected the risk of HIV transmission to the presence of STDs, NIAID has continued research into the biological, biochemical, and behavioral basis of various STDs, as well as their manifestations and potential treatments. NIAID supports STD research through grants initiated by individual investigators and through a variety of research programs. STD Cooperative Research Centers bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. The STD Clinical Trials Unit conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at STD prevention and control. The Topical Microbicides Program projects conduct basic research, product development, and clinical evaluation activities aimed at the development of female-controlled barrier methods to prevent STDs and HIV infection.

*Chlamydia trachomatis*, a bacterial pathogen, is a major cause of preventable blindness and STDs in the developing world. An estimated 3 million new infections occur each year. A major problem with controlling chlamydia is that more than 80 percent of infections are asymptomatic and frequently go undetected.[82] Researchers funded by NIAID have applied the new and highly sensitive molecular diagnostic assays to screening large populations in Baltimore, Maryland, in the U.S. military, and in Uganda and have documented extremely

high rates of infection ranging from 5 to more than 25 percent.

Approximately one in five adults in the United States have genital herpes, but only one-third of those people know they have the herpes simplex virus (HSV-2). The number of Americans with genital herpes has increased 30 percent since the 1970s. Moreover, HSV-2 prevalence among 12- to 19-year-old whites is now five times higher than it was 20 years ago. In addition, young adults ages 20 to 29 are now twice as likely to have genital herpes. Although most genital herpes cases are asymptomatic, infection still poses risks. Asymptomatic individuals can transmit HSV to others; it is believed that a pregnant woman infected with HSV can transmit the virus to her baby. Considering that between 20 and 60 percent of U.S. women of childbearing age have been infected with genital herpes, the risk of neonatal herpes is significant.[83] NIAID currently supports research on effective methods to prevent HSV infection, including antiviral drugs, monoclonal antibodies, and vaccines.

An infected pregnant woman may transmit gonorrhea to her infant as the baby passes through the birth canal during delivery. This transmission can result in gonococcal infection of the baby's eyes, throat, or respiratory tract. A high priority for NIAID is to develop tools to prevent gonorrhea, such as vaccines or topical microbicides. The recent completion of the genomic sequence of *Neisseria gonorrhoeae* will help provide new insights into the pathogenesis of gonorrhea, paving the way for opportunities for new diagnostic, drug, vaccine, and microbicide developments.

A person infected with syphilis who has not been treated may infect others during the first two stages of the disease, which usually last 1 to 2 years. In its late stages, untreated syphilis, although not contagious, can cause serious heart abnormalities, mental disorders, blindness, other neurologic problems, and death. Syphilis continues to disproportionately affect African Americans, with reported rates of primary and secondary syphilis 30 times higher for African Americans than for white Americans. Pregnant women with syphilis can pass the bacterium to their unborn children, who may be born with serious mental and physical problems as a result of this infection. NIAID is supporting a clinical research protocol examining a single oral dose of therapy for early syphilis.[84]

Topical microbicides (virus- and bacteria-killing gels, foams, creams, or films) might be more effective than condoms in killing STD pathogens, including HIV, because such preparations would be easier to use and women would not have to negotiate their use, as they often must do with condoms. NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The Institute supports six Topical Microbicide Program projects that focus on the development of these compounds and recently initiated the Microbicide Preclinical Development Program. Cosponsored by the National Institute of Child Health and Human Development, this new program supports the discovery and preclinical development of novel or underexplored microbicides.

## Additional NIAID Activities Affecting Research on Women's Health Issues

In all of its clinical research, including biomedical and behavioral studies, NIAID complies with the 1993 NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Congress mandated the establishment of these guidelines in the NIH Revitalization Act of 1993, and NIAID staff members participated in their development. The guidelines stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects, unless there is a compelling reason that such inclusion would be inappropriate. The guidelines also state that women of childbearing potential should not be routinely excluded from participation in clinical research.

## Minority Researchers' Training and Enhancement Programs

Increasing the participation of underrepresented minority investigators in virtually all fields of biomedical research is a continuing NIH and NIAID priority. In addition to supporting NIH-wide programs, NIAID has developed and supported a variety of innovative minority programs for biomedical research, encompassing high school through postdoctoral training.

OSPRT continues to administer the Introduction to Biomedical Research Program (IBRP) and the Bridging the Career Gap for Underrepresented Minorities Workshop. In October 2001, NIAID held its fifth symposium on bridging the career gap for underrepresented minority scientists. This initiative nurtures the research careers of individuals currently funded under various NIAID minority training and enhancement programs. In February 2002, NIAID will hold its 24th IBRP (www.niaid.nih.gov/ibrp). The annual 4-day program uses scientific lectures, interactions with NIAID's intramural scientists, and tours of the NIH campus to inform academically talented minority students about research career opportunities.

NIAID also collaborates with minority organizations to disseminate information about biomedical research careers to members of underrepresented groups. The Institute provides funding to the Interamerican College of Physicians and Scientists' Hispanic Youth Summer Program, which seeks to introduce Hispanic youth to careers in biomedical research through scientific seminars and field trips. NIAID also supports a segment of the "Las Hermanitas," an annual seminar conducted by MANA, Inc., that provides information about STDs, chronic diseases, and science career opportunities for Hispanic teenage girls.

NIAID continues to work with schools on several programs that foster an interest in science and research careers among younger students. The Institute supports the Partners in Education Program, which provides students in the Washington, D.C., area with a scientific environment in which they can nurture their interest in the sciences. In FY 2001, NIAID helped establish a partnership program with Temple University to foster the academic careers of outstanding minority students in middle schools. NIAID's Rocky Mountain Laboratories teamed up with

local middle schools and high schools in Montana to present a program that introduces students to biomedical research.

NIAID continues to strengthen its research on infectious and immunologic diseases that contribute to health disparities experienced by minority populations, as well as programs designed to build a new cadre of minority researchers. These efforts, coupled with the Institute's increased outreach to minority groups, will help ensure that the benefits of NIAID research are shared by all segments of our nation's population.

# Genomics

## Division of Microbiology and Infectious Diseases

Advances in molecular biology have led to remarkably fast and accurate methods for sequencing the genomes of disease-causing microorganisms. Genome sequencing reveals the lineup of paired chemical bases that make up the pathogen's DNA, the language of life. The potential payoffs of sequencing pathogens are enormous. Sequence information is being exploited in the following ways:

- To locate targets for vaccine and drug development,
- To identify mutations that contribute to drug resistance,
- To compare the genomes of variant strains to note differences that may affect the antigenicity or virulence of the microbe, and
- To trace microbial evolution.

When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes, and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Once virulence genes are found, researchers can attempt to disable them. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains, such as the spread of a virulent form of a pathogen in a susceptible population. Finally, understanding the genetic basis for both virulence and drug resistance also may help predict disease prognosis and influence the type and extent of patient care and treatment.

Recognizing the tremendous benefits of genome sequencing, NIAID has funded projects to sequence the full genomes of a number of medically important microbes, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and foodborne diseases. In addition, NIAID collaborates with other funding agencies to sequence the larger genomes of protozoan pathogens, such as that of the organism causing malaria. Many of these microbes have been sequenced and are now being annotated and analyzed. The complete genome sequence of *Plasmodium falciparum*, the parasite that causes malaria, is expected to be published in 2002 and is based on the work of the International Malaria Genome Sequencing Consortium, which NIAID supports. In addition, NIAID awarded a grant to rapidly sequence the genome of the malaria mosquito, *Anopheles gambiae*, which transmits the malaria parasite to people. The three genome sequences—the malaria mosquito, malaria parasite, and human—will provide scientists with a unique opportunity to study the natural history of malaria. For the first time, researchers will have the complete genetic information on an infectious organism, its natural host, and the insect that transmits the disease. Sequence information and annotation data that identify putative genes in the genome are continually made available to the scientific community by means of publicly accessible web sites.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics,

decoding sequence information, and determining its functional sequence. NIAID continues to collaborate with the National Institute of General Medical Sciences (NIGMS) and helps to fund two NIGMS research projects that are part of the NIGMS Protein Structure Initiative (www.nigms.nih.gov/funding/psi.html), which supports research centers in the structural genomics for both the development of high-throughput methods and structural determination of proteins. One project supports the determination and analysis of structures of more than 400 functionally relevant *Mycobacterium tuberculosis* proteins, whereas the other focuses on determining the protein structures from pathogenic protozoa.

NIAID also is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate sequence and functional data. Recently, NIAID funded a Pathogen Functional Genomics Resource Center to develop and distribute genomic resources to the research community. The Institute continues to provide support for a database of genomic and postgenomic information on sexually transmitted pathogens (www.stdgen.lanl.gov) and poxviruses (www.poxvirus.org). NIAID's pathogen genomics web site has been updated, providing details on currently supported genome-sequencing projects and on policies and priorities for large-scale genome-sequencing projects and related genomic activities (www.niaid.nih.gov/dmid/genomes).

## Division of Allergy, Immunology and Transplantation

The Division of Allergy, Immunology and Transplantation (DAIT) also supports genomics research. The human immune system is composed of complex networks of interacting cells, each programmed by precisely scripted genes. Underlying each immune response to a disease is a multistepped pathway of interacting molecules influenced by an individual's unique genomic characteristics. The immune system plays a critical role in diseases such as rheumatoid arthritis, hay fever, contact dermatitis, insulin-dependent or type 1 diabetes, systemic lupus erythematosus (SLE), and graft rejection of transplanted solid organs, tissues, and cells. Each of these diseases has an underlying genetic component.

Genomic research supported by DAIT is yielding insights into the functional and structural dimensions of immune system regulation, hypersensitivity and inflammation in diseases such as asthma, the dysregulation of immune responses that results in autoimmune disease, and basic mechanisms of immune tolerance and graft rejection. This research is important in the following areas:

- **Asthma and allergic diseases.** DAIT-supported research on the genetics of asthma, hypersensitivity, inflammation, and T-cell mediation enables us to understand the mechanisms underlying these immune responses, resulting in improved diagnostic, prevention, and treatment strategies. Through genomic research, DAIT-supported investigators discovered that interleukin-4 (IL-4), a cytokine that is produced by helper T cells and mast cells, stimulates antibody

production by B cells in a series of reactions involving several genes. Further studies on IL-4 may provide a marker for measuring asthma risk and severity.

- **Autoimmune diseases.** DAIT supports research on type 1 diabetes and other autoimmune diseases that involve more than a single gene. Recent developments in genomics, such as high-resolution DNA analysis and bioinformatics tools, are making it possible to understand the underlying genetic causes of these complex diseases. For example, one approach compares the genes of individuals with an autoimmune disease with those of healthy individuals to identify genetic and genomic differences that may be the underlying cause of disease. Between 10 and 20 distinct loci on the human genome may be responsible for susceptibility to type 1 diabetes. This knowledge will increase our ability to predict, diagnose, and treat this disease.

- **Transplantation.** DAIT-supported research on the genetics of graft rejection and immune tolerance is breaking new ground in the transplantation of solid organs, tissues, and cells for the prevention and treatment of disease. Genomic research funded by DAIT has identified surrogate markers of graft rejection in kidney transplant recipients. This research holds promise for the development of a noninvasive predictor of graft rejection based on gene expression analysis in urinary cells of transplant recipients.

- **Basic immunology research.** Basic research in immunology furthers our understanding of the properties, interactions, and functions of the cells of the immune system and the genetic aspects of immune system regulation, and provides information about essential structural immunobiology. Recent breakthroughs in the basic science of immunogenetics inform clinical immunology, which may lead to the development of new immune-based therapies. Examples of basic immunology research supported by DAIT include the following:

  – Use of large-scale gene- and protein-expression-analysis tools to describe pathways of cellular activation;

  – Discovery of anti-inflammatory and immunosuppressive agents using DNA-based screening methods; and

  – Analysis of genomic databases of T-cell receptors and immunoglobulin gene sequences to link structural, functional, and clinical information.

### *Multicenter Research Programs*

DAIT supports several multicenter research programs that include significant genomic efforts aimed at understanding the underlying mechanisms of immune-mediated diseases.

**Immune Tolerance Network (ITN).** The ITN is an international consortium of more than 70 basic scientists and clinical investigators established in FY 1999 to explore new approaches to selectively block or prevent the initiation of harmful immune responses. The potential impact of tolerance induction to improve human health is great, encompassing a broad range of immune-mediated disorders, including autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis; asthma and

allergic diseases; and graft rejection in solid organ, tissue, and cell transplantation.

Genomic research now under way in the ITN may offer new therapeutic strategies for tolerance induction. The ITN is developing clinical trials of multiple tolerance induction approaches for several autoimmune diseases, including multiple sclerosis and type 1 diabetes. The ITN also is pursuing clinical trials of multiple tolerance induction approaches for asthma and allergic diseases, and currently supports a trial of DNA-ragweed-allergen conjugates for the treatment of allergic rhinitis. The network includes core laboratories to develop diagnostic assays to measure the induction, maintenance, and loss of tolerance in humans. These core facilities will develop and perform microarray analyses of gene expression, quantitative assays of T-cell reactivity, novel tissue morphology studies to analyze tissue changes due to disease progression and therapeutic efficacy, and bioinformatics approaches to analyze clinical and scientific data sets from the ITN-sponsored clinical trials.

**Autoimmunity Centers of Excellence.** These centers support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of promising immunomodulatory therapies. The centers are presently enrolling participants in several clinical trials, including a trial of anti-CD20 in SLE and a trial of anti-C5 in lupus nephritis.

**International Histocompatibility Working Group (IHWG).** The IHWG is a network of more than 200 laboratories in more than 70 countries that applies new molecular techniques to population-based studies of histocompatibility genes. Histocompatibility genes allow the immune system to respond to specific pathogens, but these genes also play a role in the unwanted immune responses that occur in graft rejection and autoimmune diseases. Recent advances in genomics will facilitate the work of the human leukocyte antigen (HLA) class II genes and related polymorphisms and their role in immunity, disease susceptibility, and graft rejection. Genomic techniques developed by IHWG investigators and others have shown that there is a greater diversity among histocompatibility genes than was previously detected by conventional serologic methods. This work will bridge the gap between serologic and genomic definitions of these genes.

**Multiple Autoimmune Diseases Genetics Consortium (MADGC).** MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides materials to promote research aimed at discovering the human immune response genes involved in autoimmunity. MADGC began enrolling families in May 2000; to date, 121 families have been enrolled. More information can be found at www.madgc.org.

**North American Rheumatoid Arthritis Consortium (NARAC).** NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the

genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. More information can be found at http://naracdata.org. This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation.

**Primary Immunodeficiency Diseases Registry.** This registry was established by NIAID through a contract with the Immune Deficiency Foundation (IDF) to maintain clinical information on patients in the United States affected by primary immunodeficiency diseases. For each disease, the registry collects information on the natural course of the disease, including early and late complications; effects of therapy; and causes of death. The diseases included in the registry are chronic granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease (SCID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte-adhesion deficiency, and DiGeorge syndrome. Researchers may apply to the registry to obtain access to the patients for both basic research studies and clinical trials.

**Federal Government/industrial collaboration.** DAIT, in partnership with Roche Pharmaceuticals and Motorola, is supporting research projects that use bioinformatics to analyze clinical and gene-expression data that have been combined into one seamless database. This work, involving clinical data, rapid throughput polymerase chain reaction, and gene chip and proteomics data, aims to determine the underlying immune mechanisms responsible for the initiation and progression of end-stage renal disease (kidney failure), as well as acute and chronic kidney-graft rejection and long-term kidney-graft survival. This research models disease processes through a combination of sophisticated data-mining and hypothesis-based research to identify early markers of kidney-graft acceptance, rejection, and function. This government-industry collaborative effort serves as a model for future programs in other immune-mediated diseases, particularly autoimmune disorders.

DAIT is collaborating with ProSanos Corporation, a clinical informatics software firm, and Management Science Associates, Incorporated, a world leader in large-scale database construction and management, to gain new insights into the immune mechanisms of kidney-graft rejection and survival. Newly developed software facilitates analyses across several clinical, epidemiologic, and genetic databases to perform sophisticated modeling of disease processes. The results of this project will lead to a greater understanding of the underlying immune mechanisms responsible for end-stage renal disease and acute and chronic kidney-graft rejection, yielding novel targets for therapeutic interventions to prolong graft survival.

In another DAIT-sponsored effort, Bioseek of Burlingame, California, is developing advanced flow cytometric-based methods to measure the expression of cell-surface molecules on endothelial cells—cells lining especially blood and lymphatic vessels. Such data will be useful in comparing the effects of various anti-inflammatory drugs and may provide the knowledge base necessary for the development of novel anti-inflammatory drugs.

The following is a list of NIAID-supported large-scale pathogen genome-sequencing projects in FY 2001:

| Organism | Disease | Organism | Disease |
|---|---|---|---|
| • *Anopheles gambiae* | malaria | • *Rickettsia rickettsii* | Rocky Mountain spotted fever |
| • *Aspergillus fumigatus* | aspergillosis | • *Rickettsia typhi* | typhus |
| • *Bacillus anthracis* | anthrax | • *Salmonella typhi* | typhoid fever |
| • *Brucella suis* | brucellosis | • *Salmonella typhimurium* | foodborne diseases, gastritis |
| • *Brugia malayi* | elephantiasis | • *Schistosoma mansoni* | dermatitis, Katayama fever, liver inflammation, fibrosis |
| • *Buckholderia mallei* | glanders | • *Shigella flexneri* | shigellosis, hemolytic uremic syndrome |
| • *Chlamydia pneumoniae* | pneumonia | • *Staphylococcus aureus* | surgical and wound infections, pneumonia, toxic shock syndrome |
| • *Chlamydia trachomatis* | genital and chlamydia infections, trachoma | • *Staphylococcus epidermidis* | bacteremia |
| • *Clostridium perfringens* | gas gangrene | • *Streptococcus pneumoniae* | pneumonia, meningitis |
| • *Coccidioides immitis* | respiratory infections; coccidioidomycosis | • *Streptococcus pyogenes* | strep throat, scarlet fever, pharyngitis, skin infections, necrotizing fasciitis, toxic shock syndrome, rheumatic fever |
| • *Coxiella burnetii* | Q fever | • *Toxoplasma gondii* | toxoplasmosis, congenital, and ocular infections, opportunistic disease |
| • *Cryptococcus neoformans* | cryptococcosis | • *Treponema pallidum* | syphilis |
| • *Cryptosporidium parvum* | foodborne and waterborne diseases, gastritis | • *Trypanosoma brucei* | trypanosomiasis |
| • *Ehrlichia* spp. | ehrlichiosis | • *Trypanosoma cruzi* | Chagas' disease |
| • *Entamoeba histolytica* | dysentery | • *Ureaplasma urealyticum* | pelvic inflammatory disease |
| • *Enterococcus faecalis* | nosocomial infections | • *Vibrio cholerae* | cholera |
| • *Escherichia coli* 0157:H7 | gastritis, hemolytic, uremic syndrome | • *Wolbachia* | endosymbiont of filarial nematodes and insect vectors |
| • *Escherichia coli* K1 | meningitis | • *Yersinia pestis* | plague |
| • *Escherichia coli* CFTO73 | urinary tract infections | | |
| • *Giardia lamblia* | giardiasis | | |
| • *Haemophilus ducreyi* | chancroid | | |
| • *Histoplasma capsulatum* | histoplasmosis | | |
| • *Legionella pneumophila* | Legionnaire's disease | | |
| • *Leishmania major* | cutaneous leishmaniasis | | |
| • *Mycobacterium avium* | pulmonary disease, opportunistic disease | | |
| • *Mycobacterium tuberculosis* | tuberculosis | | |
| • *Neisseria gonorrhoeae* | gonorrhea | | |
| • Nematode species | helminthiases | | |
| • *Plasmodium falciparum* | malaria | | |
| • *Pneumocystis carinii* | pneumonia, opportunistic disease | | |

# Bioengineering, Bioinformatics, and Other Emerging Technologies

Bioengineering, bioinformatics, and other emerging technologies are crosscutting and facilitate research in many disciplines. Bioengineering combines physics, chemistry, and mathematics as well as basic engineering principles to enhance the study of biology, medicine, behavior, and health. Engineering principles and techniques can be applied to the development of new biologics, materials, and devices for the diagnosis, prevention, and treatment of disease. Bioinformatics and computational biology involve the application of computer science and advanced mathematics to enable integration and analyses of biological, medical, behavioral, and health data. The unique tools and approaches of bioengineering, bioinformatics, and computational biology are becoming integral components of NIAID-supported basic and clinical immunology research. Examples of NIAID research in these areas include the following:

- **Mass spectrometry for high-throughput peptide characterization.** NIAID-funded investigators are developing chemical measurement instruments for the sequence analysis of peptide antigens presented in the major histocompatibility complex. This research will lead to a high-throughput method to study self-peptides. Understanding how the body distinguishes itself from foreign (possibly harmful) agents is relevant to all immune-mediated diseases.

- **Modular gene assembly.** A new system is being developed for engineering genes on the basis of their binding and activation properties as well as their diverse features. This research will enable the formation, selection, and assembly of genes based on individual functional traits, which may lead to the development of novel therapeutic compounds, such as custom antibodies or immunosuppressants.

- **Bioinformatics for lead compound selection.** Computers enhance our ability to characterize complex molecules and understand binding patterns (e.g., ligand-receptor interaction), which may lead to the identification of potential new anti-inflammatory and immunosuppressive agents.

- **A drug-delivery system to treat immune-mediated diseases.** NIAID-funded investigators are developing an active, silicon-based delivery system that may be a useful tool for vaccines, antibiotics, and anti-inflammatory agents. Controlled delivery has the advantage of providing the appropriate amount of a drug tailored to the needs of individual patients.

- **Whole-organism imaging of immune response.** The ability to monitor the precise ways in which T cells accumulate in lymphoid organs, such as the liver, kidney, and bowel, or in the central nervous system holds important keys to understanding immune-mediated disorders (e.g., autoimmune diseases and graft rejection). For example, the monitoring of cell migration can provide an early warning of acute graft rejection in organ transplant recipients. NIAID-funded investigators are applying magnetic resonance imaging to detect accumulation of labeled T cells and macrophages in a living organism and are perfecting agents that show the contrast between cells and background tissue. One NIAID-funded project has combined nuclear and magnetic resonance imaging as a prototype system for whole-body scanning and imaging of the mouse.

Each of these developments illustrates the interdependence between the basic sciences, medicine, and the computer and engineering sciences. This interdependence is producing an infrastructure of instruments and databases that is extending the capacity of science to perceive, capture, and manage information about biological processes. Recent innovations in the emerging fields of proteomics, sensors, and data integration promise to develop this infrastructure even further and yield real benefits for researchers in the near future.

Many NIAID-funded investigators are now shifting their attention to the proteins expressed by genes. The rapidly emerging field of proteomics will soon provide a wealth of information about the characteristics of each protein, including function, structure, location, variants, and similarities to other proteins. NIAID supports efforts to develop new tools to monitor and manipulate gene expression. In FY 2001, NIAID launched a new initiative, the Bioinformatics Integration Support Contract (BISC), to (1) link genomic and other basic scientific and clinical data from a variety of sources, (2) enable scientists to easily access, generate, and exchange complex, high-quality data sets, and (3) serve the data integration and archiving needs of several large research programs supported by NIAID.

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# National Advisory Allergy and Infectious Diseases Council

The National Advisory Allergy and Infectious Diseases Council is composed of both scientists and laypersons. The Council makes final recommendations on the scientific merit of NIAID-assigned applications for research grants, cooperative agreements, and awards for research training activities. Review by the Council is the final step in the NIH peer review process. Council recommendations are based both on scientific merit, as judged by the scientific review groups, and on the relevance of the proposed study to the Institute's programs and priorities. Applications reviewed relate to all activities within the NIAID research mission, including the fields of immunology, allergic and immunologic diseases, transplantation immunology, microbiology and infectious diseases, and AIDS and AIDS-related conditions. Through its subcommittees, the Council conducts concept clearances and advises NIAID on general policy.

The National Advisory Allergy and Infectious Diseases Council roster is located at the web site www.niaid.nih.gov/facts/council.htm.

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# Acquired Immunodeficiency Syndrome Research Review Committee

In its role within the NIH peer review system, the Acquired Immunodeficiency Syndrome (AIDS) Research Review Committee advises the Directors of the NIH and NIAID with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The Committee provides a primary review of selected grant applications, cooperative agreements, and contract proposals for special research and training programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in AIDS-related areas. The Committee recommends ratings for those applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in the above-mentioned scientific areas.

The AIDS Research Review Committee roster is located at the web site www.niaid.nih.gov/facts/revcom.htm.

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# AIDS Research Advisory Committee

The AIDS Research Advisory Committee is mandated by Public Law 100-607, the Health Omnibus Programs Extension of 1988 (HOPE legislation), which was signed into law on November 4, 1988. The Committee advises and makes recommendations to the Director, NIAID, and to the Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), in all areas of biomedical research on HIV infection and AIDS related to the mission of DAIDS, including pathogenesis, natural history, and transmission of HIV disease, and to those efforts that support progress in its detection, treatment, and prevention.

The Committee provides broad scientific, programmatic, and budgetary advice on all aspects of HIV-related research supported by NIAID, including fundamental basic and clinical research, discovery and development of vaccines and other preventive interventions, and training of researchers in these activities. This activity includes the review of progress and productivity of ongoing efforts, assistance in identifying critical gaps/obstacles to progress, and approval of concepts for new initiatives.

The AIDS Research Advisory Committee roster is located online at www.niaid.nih.gov/facts/arac.htm.

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# AIDS Vaccine Research Working Group

The AIDS Vaccine Research Working Group, established in February 1997, assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine. The individuals in this group provide advice regarding the vaccine research programs at the NIH with respect to scientific opportunities, gaps in knowledge, and future directions of research. The Working Group, which reports to the NIAID Council, is chaired by Dr. David Baltimore and is composed of individuals with expertise in immunology, structural biology, virology, animal models, and vaccine development.

The AIDS Vaccine Research Working Group roster is located at the web site www.niaid.nih.gov/aidsvaccine/avrc.htm.

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University of California, San Diego
Stein Clinical Research Building, Room 327
La Jolla, California 92093

William Snow
AIDS Vaccine Advocacy Coalition
40 Alta Road
Berkeley, California 94708

Irving Weissman, M.D.
Professor of Pathology
Stanford University School of Medicine
B257 Beckman Center
Stanford, California 94305-5423

Harold Varmus, M.D. (ad hoc)
CEO and President
Memorial Sloan-Kettering Cancer Center,
20th Floor
1275 York Avenue
New York, New York 10021

# Allergy, Immunology, and Transplantation Research Committee

The Allergy, Immunology, and Transplantation Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of allergy, clinical immunology, immunopathology, immunobiology, immunogenetics, immunochemistry, and transplantation biology. The Committee provides primary review of grant applications and special research programs. These include program projects, institutional National Research Service Awards, conference grants, and special developmental award programs. The Committee recommends ratings for those applications that it determines to have significant and substantial scientific merit.

The Allergy, Immunology, and Transplantation Research Committee roster is located at the web site www.niaid.nih.gov/facts/revcom.htm#CVH16.

## Roster

***(Terms expire June 30 of the year shown.)***

Paula B. Kavathas, Ph.D. (2002)
Chair
Associate Professor
Departments of Laboratory Medicine and Genetics
School of Medicine
Yale University
New Haven, Connecticut 06520

Rafeul Alam, M.D., Ph.D. (2004)
Professor
Department of Internal Medicine
University of Texas Medical Branch
Galveston, Texas 77555-1083

Charles L. Bevins, M.D., Ph.D. (2002)
Associate Staff
Department of Immunology
Lerner Research Institute
The Cleveland Clinic Foundation
Cleveland, Ohio 44195

William J. Burlingham, Ph.D. (2005)
Associate Professor
Department of Surgery
University of Wisconsin Medical School
Madison, Wisconsin 53792-0792

Anita S. Chong, Ph.D. (2003)
Associate Professor
Departments of General Surgery, Immunology, and Microbiology
Rush University
Cohn Research Building
Chicago, Illinois 60612

Daniel H. Conrad, Ph.D. (2004)
Professor
Department of Microbiology and Immunology
Virginia Commonwealth University
Richmond, Virginia 23928

Jeffrey A. Frelinger, Ph.D. (2003)
Professor
Department of Microbiology and Immunology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina 27599-7290

Kathryn Haskins, Ph.D. (2005)
Professor
Department of Immunology
School of Medicine
University of Colorado Health Sciences Center
Denver, Colorado 80262

David P. Huston, M.D. (2003)
Cullen Chair in Immunology
Departments of Medicine, Microbiology, and Immunology
Baylor College of Medicine
Houston, Texas 77030

Fadi G. Lakkis, M.D. (2003)
Associate Professor of Medicine and Immunobiology
Section of Nephrology
Department of Medicine
Yale University School of Medicine
New Haven, Connecticut 06520-8029

Shoshana Levy, Ph.D. (2005)
Professor of Research
Departments of Medicine/Oncology
School of Medicine
Stanford University
Stanford, California 94305-5151

Nicholas W. Lukacs, Ph.D. (2005)
Associate Professor
Department of Pathology
School of Medicine
University of Michigan
Ann Arbor, Michigan 48109-0602

Larry W. Moreland, M.D. (2002)
Associate Professor of Medicine
Department of Medicine
School of Medicine
University of Alabama at Birmingham
Birmingham, Alabama 35294

Daniel L. Mueller, M.D. (2002)
Associate Professor
Center for Immunology
University of Minnesota
Minneapolis, Minnesota 55455-0392

Andre E. Nel, M.D., Ph.D. (2004)
Professor of Medicine
Department of Medicine
School of Medicine
University of California, Los Angeles
Los Angeles, California 90095-1680

Shiguang Qian, M.D. (2005)
Associate Professor
Department of Surgery
Thomas E. Starzi Transplantation Institute
University of Pittsburgh Medical School
Pittsburgh, Pennsylvania 15213

Alkis G. Togias, M.D. (2003)
Associate Professor of Medicine
Divisions of Clinical Immunology and Pulmonary and Critical Care Medicine
Johns Hopkins Asthma and Allergy Center
Johns Hopkins University
Baltimore, Maryland 21224

Anne M. VanBuskirk, Ph.D. (2004)
Assistant Professor
Department of Surgery
College of Medicine
Ohio State University
Columbus, Ohio 43210

***Scientific Review Administrator and Executive Secretary***

Nancy B. Saunders, Ph.D. (2007)
Scientific Review Administrator
Science Review Program
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892-7616

# Microbiology and Infectious Diseases Research Committee

The Microbiology and Infectious Diseases Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in microbiology and infectious diseases. Specialized areas of concern include molecular biology, microbial chemistry, parasitology, virology, bacteriology, mycology, vaccine development, and antimicrobial chemotherapy. The Committee provides a primary review of grant applications, cooperative agreements, and contract proposals for special research programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in the areas mentioned above. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in these scientific areas.

The Microbiology and Infectious Diseases Research Committee roster is located online at www.niaid.nih.gov/facts/revcom.htm#SAL32.

## Roster

***(Terms expire June 30 of the year shown.)***

Sheila A. Lukehart, Ph.D. (2002) (Chair)
Professor
Department of Medicine and Infectious Diseases
School of Medicine
University of Washington
Harborview Medical Center
Seattle, Washington 98195

Michael J. Buchmeier, Ph.D. (2005)
Professor
Department of Neuropharmacology
The Scripps Research Institute
La Jolla, California 92037

Henry F. Chambers, M.D. (2002)
Professor
Department of Medicine
School of Medicine
University of California, San Francisco
San Francisco, California 94143

John Hay, Ph.D. (2002)
Grant T. Fisher Chair and Professor
Department of Microbiology
School of Medicine and Biomedical Sciences
State University of New York at Buffalo
Buffalo, New York 14214

Randall K. Holmes, M.D., Ph.D. (2004)
Professor and Chair
Department of Microbiology
University of Colorado Health Sciences Center
Denver, Colorado 80262

Clifford W. Houston, Ph.D. (2003)
Professor
Department of Microbiology and Immunology
School of Medicine
University of Texas Medical Branch
Galveston, Texas 77555

Karla A. Kirkegaard, Ph.D. (2002)
Professor
Department of Microbiology and Immunology
School of Medicine
Stanford University
Stanford, California 94395

Jean C. Lee, Ph.D. (2003)
Associate Professor
Department of Medicine
Channing Laboratory
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts 02115

Anna Suk-Fong Lok, M.D. (2002)
Professor
Division of Gastroenterology
Department of Internal Medicine
University of Michigan Medical Center
Ann Arbor, Michigan 48109

Diane M. McMahon-Pratt, Ph.D. (2004)
Professor
Department of Epidemiology and Public Health
Yale University School of Medicine
New Haven, Connecticut 06510

Thomas G. Mitchell, Ph.D. (2003)
Associate Professor
Department of Microbiology
School of Medicine
Duke University Medical Center
Durham, North Carolina 27710

William A. Petri, Jr., M.D., Ph.D. (2005)
Professor
Department of Medicine and Infectious Diseases
University of Virginia Health System
Charlottesville, Virginia 22908

John J. Treanor, M.D. (2004)
Professor
Department of Infectious Diseases Unit
University of Rochester School of Medicine
Rochester, New York 14642

Christopher C. Whalen, M.D. (2003)
Associate Professor
Department of Epidemiology and Biostatistics
School of Medicine
Case Western Reserve University
Cleveland, Ohio 44106

***Scientific Review Administrator***

Gary Madonna, Ph.D.
Microbiology and Infectious Diseases Research Committee
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

# Board of Scientific Counselors

The Board of Scientific Counselors advises the Director, NIH, the Deputy Director for Intramural Research, NIH, the Director, NIAID, and the Director, Division of Intramural Research (DIR), NIAID, concerning the Institute's intramural research programs. The Board's recommendations are based on rigid and objective reviews of NIAID laboratories to assess ongoing research, as well as future directions, and to evaluate the productivity and performance of NIAID's tenured scientists, tenure-track scientists, and the Scientific Director. Following each review, the written report from the Board is forwarded, with a response from the Director, DIR, NIAID, to the Deputy Director for Intramural Research, NIH. In addition, the Board's recommendations are communicated annually to the National Advisory Allergy and Infectious Diseases Council.

The Board's review process strengthens NIAID's tenure system and the overall quality of the Institute's research. As a result of the Board's scientific review, NIAID may modify or redirect its intramural research priorities to allow for scientific growth of investigators as well as pursuit of important new areas of research. Its findings have a direct impact on the allocation of personnel, budget, and space resources within each laboratory.

The Board of Scientific Counselors roster is located at the web site www.niaid.nih.gov/facts/bscroste.htm.

## Roster

***(Terms expire June 30 of the year shown.)***

J. Donald Capra, M.D. (2002) (Chair)
President and Scientific Director
Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma 73104

Frances M. Brodsky, D.Phil. (2004)
Professor
Department of Pharmacy and Pharmaceutical Chemistry
Department of Microbiology and Immunology
Hooper Foundation
University of California at San Francisco
San Francisco, California 94143

Irma Gigli, M.D. (2002)
Professor of Medicine
Institute of Molecular Medicine for the Prevention of Human Diseases
University of Texas Health Science Center at Houston
Houston, Texas 77030

George V. Hillyer, Ph.D. (2004)
Chancellor
University of Puerto Rico, Rio Piedras Campus
Professor and Director
Laboratory of Parasite Immunology and Pathology
Department of Pathology and Laboratory Medicine
University of Puerto Rico School of Medicine
San Juan, Puerto Rico 00936-5067

Elliott D. Kieff, M.D., Ph.D. (2003)
Harriet Ryan Albee Professor
Department of Medicine, Microbiology, and Molecular Genetics
Channing Laboratory
Brigham and Women's Hospital
Harvard University
Boston, Massachusetts 02115

Robert S. Munford, M.D. (2004)
Jan and Henri Bromberg Chair in Internal Medicine
Professor of Microbiology
Infectious Disease Division
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas 75390-9113

Barbara A. Osborne, Ph.D. (2005)
Professor
Department of Veterinary and Animal Sciences
University of Massachusetts
Amherst, Massachusetts 01003

Richard J. Whitley, M.D. (2004)
Loeb Chair in Pediatrics
Professor of Pediatrics, Microbiology, and Medicine
Department of Pediatrics
Children's Hospital
University of Alabama at Birmingham
Birmingham, Alabama 35233

***Executive Secretary***

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20892

# NIAID Executive Committee

The Executive Committee is the senior internal policy and advisory group to the Director, NIAID, and acts as a forum for discussing and setting important Institute-wide scientific and management policies and for discussing special issues and concerns that affect NIAID programs. As such, the Executive Committee consists of NIAID senior scientific and management staff, as well as several ad hoc members who provide program-staff-level input. All new, expansion, and renewal program initiatives are reviewed by the Executive Committee at the earliest possible stage of project development to provide the NIAID Director and senior staff the opportunity to discuss and consider the merit and relationship of all projects to the ongoing programs of the Institute. The Executive Committee also serves as the vehicle for senior NIAID management to communicate with Institute program staff regarding issues and policies that are being considered for implementation at both the NIAID and NIH levels.

The Executive Committee roster is located at the web site www.niaid.nih.gov/facts/executivecom.htm.

## Roster

Anthony S. Fauci, M.D. (Chair)
Director

John R. La Montagne, Ph.D.
Deputy Director

Lynn C. Hellinger
Associate Director for Management and Operations

Mark Dybul, M.D.
Assistant Director for Medical Affairs

Leslie Fink
Director
Office of Communications and Public Liaison

Gregory K. Folkers
Senior Public Affairs Advisor
Office of the Director

Richard Freed
Director
Office of Management for New Initiatives

Carole A. Heilman, Ph.D.
Director
Division of Microbiology and Infectious Diseases

Milton J. Hernandez, Ph.D.
Director
Office of Special Populations and Research Training

Elizabeth A. Holmes
Acting Director
Office of Human Resources Management

Jack Killen, M.D.
Assistant Director for Biodefense Research
Office of the Director

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research

H. Clifford Lane, M.D.
Director
Office of Clinical Research

John J. McGowan, Ph.D.
Director
Division of Extramural Activities

Michael Mowatt, Ph.D.
Director
Office of Technology Development

Gary Nabel, M.D., Ph.D.
Director
Vaccine Research Center

Roger E. Pellis
Executive Officer and Director
Office of Administrative Services

Daniel Rotrosen, M.D.
Director
Division of Allergy, Immunology and Transplantation

Karen Santoro, J.D.
Director
Office of Ethics

Ralph Tate
Director
Office of Financial Management

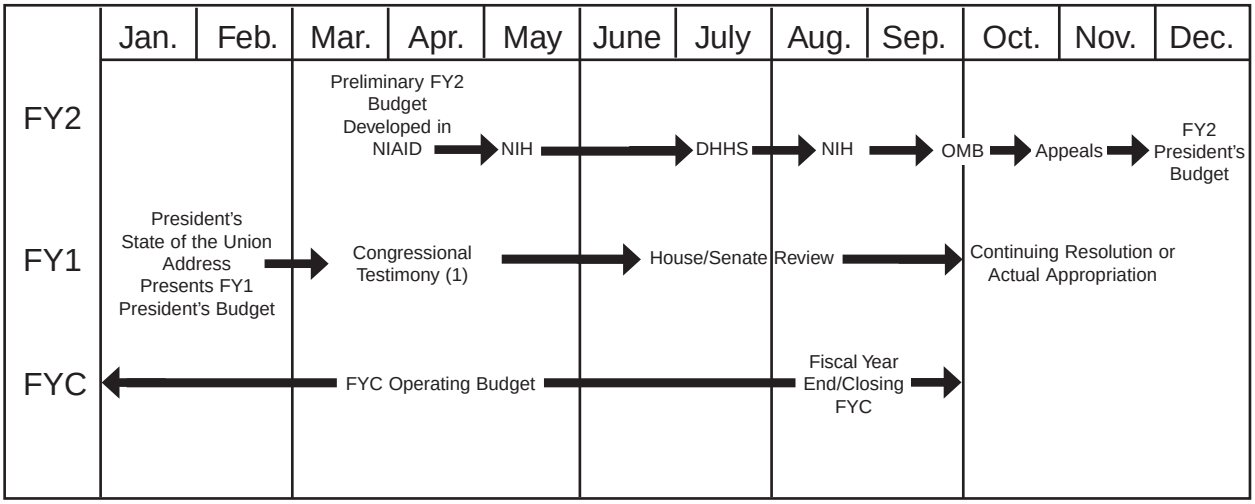
Ed Tramont, M.D.
Director
Division of Acquired Immunodeficiency Syndrome

Karl A. Western, M.D., D.T.P.H.
Assistant Director for International Research
Office of the Director

Laurence B. Wolfe, Ph.D.
Director
Office of Technology Information Systems

Vacant
Director
Office of Policy Analysis

# Federal Budget Process

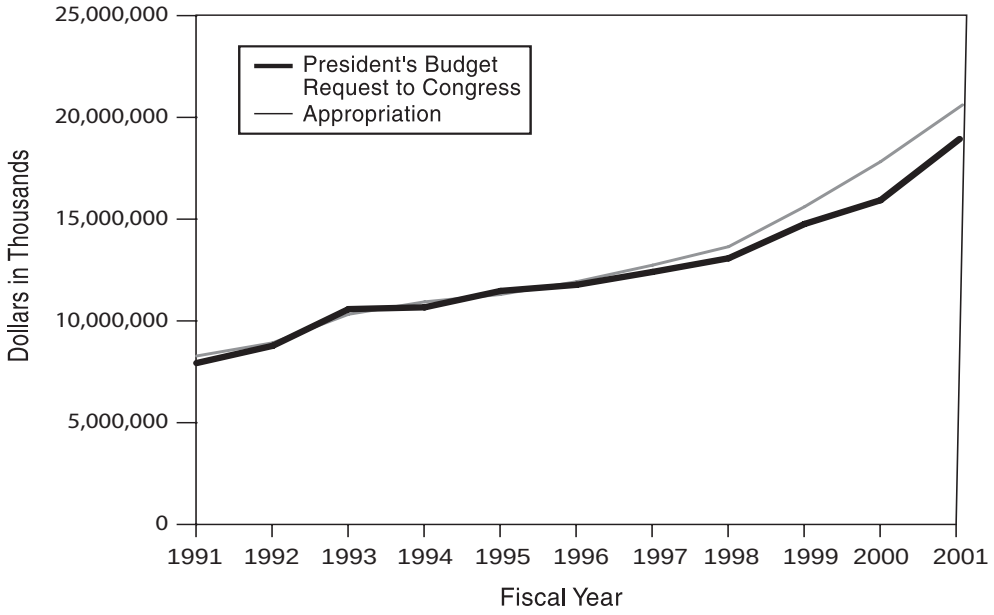



Fiscal year = October 1 to September 30

FY2 = second future fiscal year
FY1 = first future fiscal year
FYC = current fiscal year

(1) NIH Director and NIH IC Directors, including Director, NIAID, provide congressional testimony to the House and Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education.

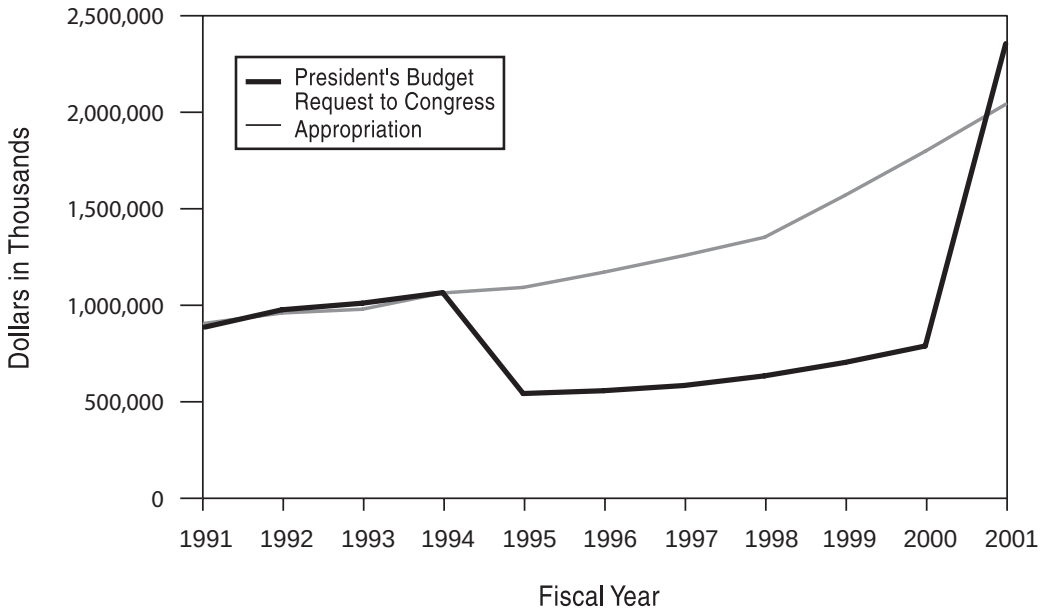
# NIH Appropriations History: FY 1991–2001




| Fiscal Year | President's Budget Request to Congress | House Allowance | Senate Allowance | Appropriation[a] |
|---|---|---|---|---|
| | | (Dollars in Thousands) | | |
| 1991 | 7,929,686,000 | 8,317,654,000 [b] | 8,347,085,000 | 8,276,632,000 [c] |
| 1992 | 8,774,886,000 | 8,824,886,000 | 8,978,133,000 | 8,921,687,000 [d] |
| 1993 | 10,579,684,000 | 10,368,551,000 | 10,387,721,000 | 10,326,604,000 [e] |
| 1994 | 10,667,984,000 | 10,936,652,000 | 10,956,389,000 | 10,937,653,000 [f] |
| 1995 | 11,473,000,000 | 11,322,023,000 | 11,333,181,000 | 11,299,522,000 [g] |
| 1996 | 11,773,066,000 | 11,939,001,000 | 11,639,204,000 | 11,927,562,000 [h] |
| 1997 | 12,406,300,000 [i] | 12,747,203,000 | 12,414,580,000 [j] | 12,740,843,000 [k] |
| 1998 | 13,078,203,000 [l] | 13,505,294,000 | 13,692,844,000 | 13,647,843,000 [m] |
| 1999 | 14,763,313,000 [n] | 14,862,023,000 | 15,622,385,000 | 15,612,386,000 [o] |
| 2000 | 15,932,786,000 | 16,936,314,000 | 17,613,470,000 | 17,826,571,000 |
| 2001 | 18,812,735,000 | 20,512,735,000 | 20,512,735,000 | 20,361,130,000 |

[a] Reflects enacted supplementals, rescissions, and reappropriations.
[b] Excludes $304,814,000 not considered.
[c] Reflects enacted administrative reduction of $29,909,000 for salaries and expenses and $205,134,000 associated with the 2.41 percent across-the-board reduction; includes sequester of $107,000.
[d] Reflects enacted administrative reduction of 69,603,000 for salaries and expenses, a travel reduction of $5,984,000, and a rescission of $13,131,000.
[e] Reflects enacted administrative reductions of an across-the-board 0.8 percent of $83,571,000, $34,857,000 for salaries and expenses, and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.
[f] Reflects a salaries and expense rescission of $18,120,000. Excludes $1,000,000 supplemental in NCRR for earthquake relief.
[g] Includes $1,299,328,000 for NIH research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of $7,446,000 for procurement, $345,000 for rent and $4,401,000 for bonus pay, and rescission of $10,000,000 in NCRR for construction and $12,384,000 in administrative costs.
[h] Includes $1,410,925,000 appropriated to the ICDs for HIV research. Incorporates the NIH share of the governmentwide administrative cost rescission ($5,780,000) and the Labor/HHS/Education bonus pay rescission ($5,659,000).
[i] Includes $1,431,908,000 for HIV research in the NIH Office of AIDS Research.
[j] Includes $1,460,312,000 for HIV research in the NIH Office of AIDS Research.
[k] Includes $1,501,073,000 for HIV research in the NIH Office of AIDS Research. Incorporated the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000).
[l] Includes $1,540,765,000 for HIV research in the NIH Office of AIDS Research.
[m] Includes $1,607,053,000 appropriated to the ICs for HIV research.
[n] Reflects a decrease of $34,530,000 for the budget amendment for bioterrorism. Includes $1,728,099,000 for HIV research in the NIH Office of AIDS research.
[o] Includes $1,798,424,000 appropriated to the ICs for HIV research.

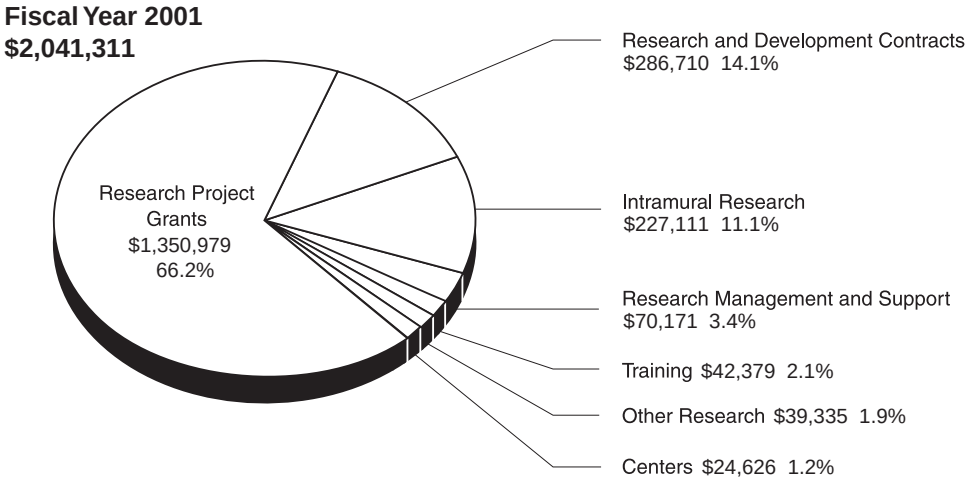
# NIAID Appropriations History: FY 1991–2001

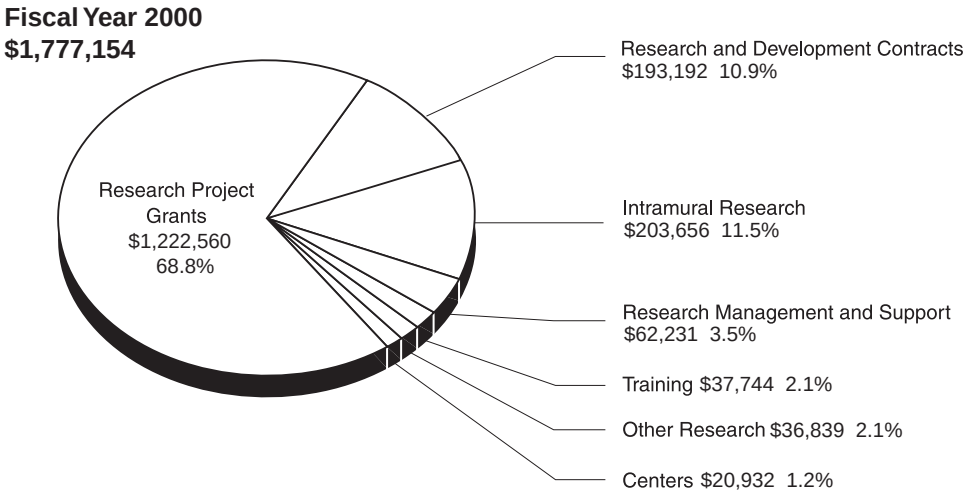



| Fiscal Year | President's Budget Request to Congress | House Allowance | Senate Allowance | Appropriation[a] |
|---|---|---|---|---|
| | | (Dollars in Thousands) | | |
| 1991 | 886,875 | 944,965 | 904,010 | 906,239 [b] |
| 1992 | 976,711 | 972,830 | 965,952 | 959,914 [c] |
| 1993 | 1,010,845 | 990,055 | 989,055 | 979,471 [d] |
| 1994 | 1,065,583 | 1,065,583 | 1,065,583 | 1,063,704 [e] |
| 1995 | 542,864 [f] | 1,094,633 | 1,094,633 | 1,092,507 [g] |
| 1996 | 557,354 [f] | 1,169,628 | 1,139,326 | 1,171,168 [h] |
| 1997 | 584,362 [f] | 1,256,149 | 1,229,009 | 1,257,794 [i] |
| 1998 | 634,272 [f] | 1,339,459 | 1,359,688 | 1,352,119 [j] |
| 1999 | 703,723 [f,k] | 1,470,460 | 1,540,102 | 1,569,063 |
| 2000 | 789,156 | 1,694,019 | 1,786,718 | 1,797,988 [l] |
| 2001 | 2,355,325 | 2,337,204 [m] | 2,375,836 | 2,041,311 |

[a] Reflects enacted supplementals, rescissions, and reappropriations.
[b] Excludes an enacted administrative reduction of $26,986,000; includes sequester of $12,000.
[c] Excludes an enacted administrative reduction of $11,197,000.
[d] Excludes an enacted administrative reduction of $12,334,000.
[e] Includes rescission of $1,879,000.
[f] Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
[g] Includes a rescission of $1,293,000 and a transfer of $458,000.
[h] Includes an enacted administrative reduction of $1,145,000 and a net NIH Director's transfer of $2,685.
[i] Includes a rescission of $575,000 for administrative expenses and a net positive transfer of $1,135,000 from the NIH Director's Reserve.
[j] Includes rescissions and transfers.
[k] Reflects an increase of $1,683,000 for the budget amendment for bioterrorism.
[l] Includes a rescission amount of $5,075,000.
[m] Represents program level.

# NIAID Funding by Budget Mechanism: FY 2000–2001




| Budget Mechanism | FY 2001[a] | % of Total | FY 2000[a] | % of Total | % Change |
|---|---|---|---|---|---|
| Research Project Grants (RPGs) | | | | | |
| Noncompeting | $990,590 | | $775,572 | | |
| Competing | 360,389 | | 446,988 | | |
| Subtotal, RPGs | 1,350,979 | 66.2 | 1,222,560 | 68.8 | +10.5 |
| Centers | 24,626 | 1.2 | 20,932 | 1.2 | +17.7 |
| Other Research | 39,335 | 1.9 | 36,839 | 2.1 | +6.8 |
| Training | 42,379 | 2.1 | 37,744 | 2.1 | +12.3 |
| R&D Contracts | 286,710 | 14.1 | 193,192 | 10.9 | +24.8 |
| Subtotal, Extramural | 1,744,029 | | 1,511,267 | | +15.4 |
| Intramural Research | 227,111 | 11.1 | 203,656 | 11.4 | +11.6 |
| Research Management and Supp. | 70,171 | 3.4 | 62,231 | 3.5 | +12.8 |
| **Total** | **$2,041,311** | | **$1,777,154** | | **+14.9** |

[a] Dollars in thousands and reflects “actuals” versus appropriations.

# NIAID Funding by the FY 2001 NIH Plan for HIV-Related Research[a] (Dollars in Thousands)

| | FY 2001 Actual | |
|---|---|---|
| | **Amount** | **Percent of Total** |
| I. Natural History and Epidemiology | 115,496 | 11.1 |
| II. Etiology and Pathogenesis | 287,790 | 27.6 |
| III. Therapeutics | 359,890 | 34.5 |
| IV. Vaccines | 207,859 | 19.9 |
| V. Behavioral Research | 16,820 | 1.6 |
| VI. Training and Infrastructure | 36,112 | 3.4 |
| VII. Information Dissemination | 20,259 | 1.9 |
| Total Funding by the FY 2001 Plan | 1,044,226 | 100 |

[a] A comprehensive plan for HIV-related research developed by the NIH Office of AIDS Research and the NIH Institutes and Centers.

# Legislative Chronology

**November 1, 1948**—The National Microbiological Institute was established under authority of section 202 of the Public Health Service Act, as implemented by General Circular No. 55, Organization Order No. 20, dated October 8, 1948.

**December 29, 1955**—NIAID was established (replacing the National Microbiological Institute) under authority of the Omnibus Medical Research Act (Public Law 81-692, 64 Stat. L. 443), as implemented by a Public Health Service Briefing Memorandum of November 4, 1955, from the Surgeon General to the Secretary of Health, Education, and Welfare.

**November 4, 1988**—NIAID was provided with additional authorities for AIDS research under Title II of the Health Omnibus Programs Extension of 1988 (HOPE legislation) (Public Law 100-607), the first major law to address AIDS research, information, education, and prevention.

**August 14, 1991**—The Public Health Service Act was amended by Public Law 102-96, the Terry Beirn Community-Based AIDS Research Initiative Act of 1991, which reauthorized NIAID's Community Programs for Clinical Research on AIDS (CPCRA). CPCRA was renamed in honor of Mr. Beirn (an AIDS activist and congressional staffer who died in 1991) and was reauthorized for an additional 5 years.

**June 10, 1993**—The Public Health Service Act was amended by Public Law 103-43, the National Institutes of Health Revitalization Act of 1993. This comprehensive legislation required NIAID to include research on tropical diseases in its mission statement and directs the Secretary, U.S. Department of Health and Human Services, to ensure that individuals with expertise in chronic fatigue syndrome or neuromuscular diseases are appointed to appropriate NIH advisory committees.

**December 14, 1993**—The Preventive Health Amendments of 1993 were passed, which included provisions requiring the Director, NIAID, to conduct or support research and research training regarding the cause, early detection, prevention, and treatment of tuberculosis. (The Institute already had authority to conduct such research under its authorities in Title IV, Public Health Service Act.)

**November 29, 1999**—The FY 2000 Appropriations Act (Public Law 106-113) established the NIH Challenge Grants program to promote joint ventures between the NIH and the biotechnology, pharmaceutical, and medical device industries. A one-time funding level of $20 million was provided within the Public Health and Social Services Emergency Fund.

**October 17, 2000**—The Children's Health Act (Public Law 106-310) required the Directors of NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases to expand and intensify the activities of their Institutes with respect to research and related activities concerning juvenile arthritis and related conditions.

**November 13, 2000**—The Public Health Improvement Act (Public Law 106-505) authorized the NIAID Director to establish a program of clinical research and training awards for sexually transmitted diseases.

### *Previous Directors*

Victor H. Haas, M.D., 1948-1957
Justin M. Andrews, Sc.D., 1957-1964
Dorland J. Davis, M.D., D.P.H., 1964-1975
Richard M. Krause, M.D., 1975-1984

# NIAID-Supported Repositories

NIAID's intramural and extramural researchers have developed an ample supply of resources and reagents that are used by scientists worldwide for basic research, applied research to develop therapeutics and vaccines, and commercialization. These resources include peptides, cell lines, monoclonal antibodies, viral vectors, and animal models.

## Division of Acquired Immunodeficiency Syndrome

### *Biological Reagents and Reference Standards*

The AIDS Research and Reference Reagent Program acquires and distributes state-of-the-art reagents for AIDS-related research and makes these reagents available to qualified investigators throughout the world. It has grown significantly during the past 13 years, and it now has more than 3,200 reagents for public distribution. The AIDS Research and Reference Reagent Program also encourages and facilitates technology transfer through workshops, publication of methods, and provision of standardized panels and protocols; facilitates commercial development of reagents; and participates as an AIDS Collaborating Center of the World Health Organization. Additional information is available at www.aidsreagent.org.

Through the Vaccine Reagent Resource, the Division of Acquired Immunodeficiency Syndrome (DAIDS) also provides resources for the production or procurement of reagents essential for vaccine studies conducted by the HIV Vaccine Trials Network (HVTN) and the Simian Vaccine Evaluation Units (SVEUs), as well as other priority vaccine studies. These resources also provide for the quality assurance testing of reagents. Additional information is available at www.niaid.nih.gov/daids/vaccine/reagentres.htm.

### *Human HIV Specimens*

Research on HIV transmission and disease progression patterns greatly benefits from a centralized system for receiving, cataloging, storing, and distributing samples collected from various well-characterized cohorts of HIV-infected individuals. NIAID provides state-of-the-art storage and computerized inventory management of specimens from domestic and international HIV epidemiology studies, HIV therapeutic and vaccine trials, and other prevention research studies through its central repositories. By making these specimens available to the scientific community, DAIDS fosters collaboration among scientific investigators to promote further progress in the detection, treatment, and prevention of HIV disease.

## Division of Allergy, Immunology and Transplantation

### *Hybridoma Cell Line Repository and Data Bank*

The Division of Allergy, Immunology and Transplantation (DAIT) has supported a project to acquire, characterize, maintain, and distribute hybridoma cell lines for more than a decade. The hybridoma cell line repository comprises more than 200 tested and frozen hybridoma cell lines, including all the lines that produce major widely used monoclonal antibody reagents.

In addition to the repository, the project includes a data bank with more than 30,000

records; each record is a complete description of a unique hybridoma, monoclonal antibody, or product of an immunoclone. The information is accessible online through a gateway provided by the Microbial Strain Data Network. Other nodes of the network exist in Japan, Europe, Canada, and India.

### *National MHC Tetramer Core Facility*

In FY 1998, NIAID established a contract facility to provide researchers with peptide-major histocompatibility complex (MHC) tetrameric molecules for analyzing antigen-specific T-cell responses. Because T cells are central to virtually all immune responses, this technology is applicable to studies in many areas, including basic immune mechanisms, infectious diseases, vaccination, auto-immunity, transplant rejection, and tumor therapy. By centralizing the production of these tetramers, individual, defined peptide-MHC molecules can be produced economically and be made available to investigators at greatly reduced expense. The MHC tetramer core facility is located at Emory University in Atlanta, Georgia, under the direction of Dr. John Altman.

## Division of Intramural Research

### *Transgenic and Gene-Targeted Mice Repository*

The Division of Intramural Research (DIR), in collaboration with DAIT, supports facilities for the acquisition, breeding, and distribution of transgenic and gene-targeted (knockout) mice, which are mice that are genetically engineered to serve as animal models for human diseases that do not occur in nonhuman species. The repository provides these mice to both intramural and extramural investigators through the NIAID/Taconic exchange for use in research and for development of clinical therapies in various infectious and immunologic diseases.

## Division of Microbiology and Infectious Diseases

### *Leprosy Research Support and Armadillo Colony Maintenance*

Although the prevalence of leprosy has declined significantly because of multidrug therapy, leprosy remains a problem worldwide. A major obstacle to leprosy research, however, is the difficulty in culturing *Mycobacterium leprae*, the organism responsible for leprosy. To overcome this problem, the Division of Microbiology and Infectious Diseases (DMID) supports the maintenance of an armadillo colony, the best animal model system of *M. leprae* infection. DMID also funds a repository of viable *M. leprae* and purified, defined reagents derived from *M. leprae*, which are available to researchers worldwide.

### *Parasitic Disease Research Support*

DMID supports three research repositories that supply parasitic organisms whose life cycles are typically too costly or too difficult for investigators to maintain in their own laboratories.

**Schistosomiasis and Filariasis Research Repositories.** The schistosomiasis repository provides qualified requesters with rodent-definitive hosts and with snail intermediate hosts infected with *Schistosoma mansoni, S. japonicum*, and *S. haematobium*. The filariasis repository provides rodent-definitive hosts and mosquito intermediate hosts infected with *Brugia malayi*, *B. pahangi*, or *Dirofilaria*

*immitis*. Organisms are provided free of charge, except for shipping costs, to both NIH-supported and independent investigators.

**Malaria Research and Reference Reagent Repository.** The malaria repository has been established to acquire, produce, and distribute malaria research reagents, reference materials, and other information to qualified investigators throughout the world. A major component of the program is the quality control of reagents, standardization of protocols, and exploration of new technologies. International workshops and training sessions will be organized to stimulate and support both laboratory-based and field-based research. The long-term goal of the repository program is to promote technology transfer as well as to facilitate research leading to commercial development of reagents for malaria diagnostics, prevention, and treatment. NIAID has established the repository in support of the Multilateral Initiative on Malaria, a research capacity-strengthening program in partnership with other national and international organizations.

### *Pneumococcal Reference Laboratory*

This laboratory provides reference and resource services and expertise to facilitate the evaluation of improved pneumococcal vaccine. A major objective is to establish a consensus assay and to improve and modify procedures for measuring antibody activity to pneumococci. The laboratory also provides radiolabeled polyribosylribose phosphate (PRP) and/or suitably derivatized PRP and purified PRP to laboratories for the performance of *Haemophilus influenzae* type b assays and for calibration of immunodiagnostic assays.

### *Repository for Biological Reagents and Reference Standards*

This repository stores and distributes serological and microbiological reagents for use as reference standards and for research in infectious and immunologic diseases. As a WHO Collaborating Center for Antiviral Drugs and Interferon, the NIAID Repository is responsible for the storage and worldwide distribution of WHO International Interferon Standards and Reference Reagents.

### *Tuberculosis Research Materials and Vaccine Testing*

*Mycobacterium tuberculosis*, the organism responsible for tuberculosis (TB), is difficult and time-consuming to grow and, because it is transmitted via aerosols, should be studied only in appropriate biohazard facilities. DMID funds a repository to provide *M. tuberculosis*-derived materials to qualified TB investigators worldwide in basic and clinical research areas, allowing work to begin quickly and eliminating the need for these investigators to have their own biohazard facilities. DMID also funds the screening, in established, small-animal, low-dose, aerosol-challenge models, of potential antituberculosis vaccine candidates provided by individual researchers.

# NIH Extramural Funding Mechanisms Used by NIAID

**F31** Predoctoral Individual National Research Service Award (NRSA)—provides predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

**F32** Postdoctoral Individual NRSA—provides postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

**F33** NRSA for Senior Fellows—provides opportunities for experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, or to acquire new research capabilities.

**F35** Intramural NRSA Individual Postdoctoral Program—supports a postdoctoral trainee in the NIH intramural program.

**K02** Independent Scientist Award—provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.

**K08** Clinical Investigator Award—provides the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who will pursue research aspects of categorical areas applicable to the awarding unit, and aids in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.

**K22** Career Transition Award—provides support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two-phase program: an initial period involving an intramural appointment of the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator to sustain or promote a successful research career.

**K23** Mentored Patient-Oriented Research Career Development Award—provides support for the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a 3-year minimum up to a 5-year period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators.

**K24** Midcareer Investigator Award in Patient-Oriented Research—provides support for experienced clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators.

**K25** Mentored Quantitative Research Career Development Award—supports junior-faculty-level investigators with

quantitative scientific and engineering backgrounds outside of biology or medicine who have the potential to integrate their expertise with biomedicine and to develop into productive investigators with a period of mentored study and research.

**K30** Clinical Research Curriculum Award (CRCA)—awarded to institutions to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. This award is intended to support the development of new didactic programs in clinical research at institutions that do not currently offer such programs or in institutions with existing didactic programs in clinical research to support or expand their programs or to improve the quality of instruction.

**N01** Research and Development Contract—develops or applies new knowledge or tests, screens, or evaluates a product, material, device, or component for use by the scientific community.

**P01** Research Program Project—provides a qualified institution on behalf of a principal investigator with the support of a broadbased, multidisciplinary, often long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources necessary for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

**P30** Center Core Grant—supports shared resources and facilities for categorical research by a number of investigators from different disciplines who provide a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem. Although funded independently of the center's component projects or program projects, the core grant relates integratively to them. By providing more accessible resources, this support is expected to ensure greater productivity than that obtained from the separate projects and program projects.

**P50** Specialized Center—supports any part of the full range of R&D, from basic to clinical, and may involve ancillary supportive activities, such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical problem area. These grants differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers also may serve as regional or national resources for special research purposes.

**R01** Research Project Grant (traditional)—provides support to an institution (domestic or foreign) on behalf of a principal investigator for a discrete project related to the investigator's interests and competence. Most of the research that the NIH supports is maintained through this support mechanism. Although rare, such a grant may be awarded directly to an individual.

**R03** Small Grant—provides research support specifically limited in time and amount for studies in categorical program areas. Small grants provide flexibility for initiating studies, which are generally for preliminary short-term projects and are nonrenewable.

**R13** Conference Grant—provides funding for conferences to coordinate, exchange, and disseminate information related to program interests. In general, such awards are modest and limited to participation with other organizations in the support of conferences rather than as a provision of sole support. Among the costs eligible for support are salaries, equipment rental, travel, consultant services, and supplies. Prospective applicants should inquire in advance concerning possible interest on the part of an Institute.

**R15** Academic Research Enhancement Award (AREA)—provides support to scientists at eligible domestic institutions for small-scale, new, or expanded health-related research projects, such as pilot research projects and feasibility studies; development, testing, and refinement of research techniques; secondary analysis of available data sets; and similar discrete research projects that demonstrate research capability. This award is directed toward smaller, less-prominent 4-year public and private colleges and universities that provide undergraduate training for a significant number of U.S. research scientists but have not had an adequate share in the growth of the NIH extramural program.

**R18** Research Demonstration and Dissemination Project—provides support to develop, test, and evaluate health-service activities and to foster the application of existing knowledge for the control of categorical diseases.

**R21** Exploratory/Developmental Grant—used by NIAID for Bridge awards. The Bridge award provides support for a limited time and amount to investigators to enable them to continue meritorious research and improve the competitiveness of future grant applications.

**R24** Resource-Related Research Project—supports research projects that will enhance the capability of resources to serve biomedical research.

**R25** Education Project—provides support to develop or implement a program in education, information, training, technical assistance, coordination, or evaluation.

**R33** Exploratory and Developmental Grants, Phase II—provide a second phase of

support for innovative, exploratory, and developmental research begun as an R21 award. Only R21 awardees are eligible to apply for R33 support. Applications are accepted only in response to RFAs and PAs that specify the R33 mechanism.

**R37** Method to Extend Research in Time (MERIT) Award—provides long-term, stable support to investigators who are likely to continue to perform in an outstanding manner and spares them the administrative burdens associated with preparing and submitting research grant applications. An initial 5-year award is accompanied by an opportunity for a 3- to 5-year extension, based on an expedited review of the accomplishments during the initial award period. Investigators may not apply for a MERIT award. NIH staff and advisors base their selection of MERIT award recipients on competing R01 applications, prepared and submitted in accordance with NIH procedures. MERIT awards are awarded to a limited number of selected investigators who have demonstrated superior competence and outstanding productivity during previous research endeavors.

**R41** Small Business Technology Transfer
**R42** (STTR) Grants—support cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.

**R43** Small Business Innovation Research
**R44** (SBIR) Grants—enable small businesses possessing technological expertise to contribute to the R&D mission of the NIH. Phase I (R43) grants support projects, limited in time and amount, to establish the technical merit and feasibility of R&D ideas that ultimately may lead to commercial products or services. Phase II (R44) grants support in-depth development of R&D ideas whose feasibility has been established in phase I and that are likely to result in commercial products or services. The research must be conducted in the United States.

**T32** Institutional NRSA—enables institutions to grant NRSAs for predoctoral and postdoctoral research training in specified shortage areas to individuals selected by the institutions.

**T35** NRSA Short-Term Research Training—provides individuals with research training during off-quarters or summer periods to encourage research careers or research in areas of national need.

**U01** Research Project (Cooperative Agreement)—provides an assistance relationship between the NIH and a recipient, but with substantial programmatic involvement by the NIH. The NIH assists, supports, or stimulates the recipients and is involved substantially with recipients in conducting projects similar in program content to those for grants, with the NIH playing a "partner" role in the effort.

**U09** Scientific Review and Evaluation (Cooperative Agreement)—provides the chairperson of an Initial Review Group with administrative funds for operation of the review group.

**U19** Research Program (Cooperative Agreement)—supports a research program of multiple projects directed toward a specific major objective, basic theme, or program goal, requiring a broadbased, multidisciplinary, and often long-term approach.

**U24** Resource-Related Research Projects/Cooperative Agreements—support research projects contributing to improvement of the capability of resources to serve biomedical research.

**U42** Animal (Mammalian and Nonmammalian) Model and Animal and Biomedical Materials Resource Cooperative Agreements (NCRR)—develop and support an animal (mammalian and nonmammalian) model or animal or biological materials resources available to all qualified investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program. Nonmammalian resources include nonmammalian vertebrates, invertebrates, cell systems, and nonbiological systems.

**UC1** NIH Challenge Grants and Partnerships Program, Phase II, Cooperative Agreements (NIAID)—promote joint ventures between the NIH and both domestic and global entities to facilitate rapid biomedical or biotechnology R&D for infectious diseases to benefit public health; projects should have a commercial potential that could not have been attained without matching funds.

**Y01** NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides a source of funds to another Federal organization outside DHHS to acquire specific products, services, or studies.

**Y02** NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides funds to another NIH component or to another organization within DHHS to acquire specific products, services, or studies.

# Acronyms

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|---|---|
| **AACTG** | Adult AIDS Clinical Trials Group |
| **ABC** | Assistance in Building Capacity (FIC) |
| **ACE** | Autoimmunity Centers of Excellence |
| **ADCC** | Autoimmune Diseases Coordinating Committee |
| **ADMO** | Associate Director for Management and Operations |
| **AIDS** | acquired immunodeficiency syndrome |
| **AIEDRP** | Acute HIV Infection and Early Disease Research Program |
| **AREA** | Academic Research Enhancement Award |
| **ART** | antiretroviral therapy |
| **AVEG** | AIDS Vaccine Evaluation Group |
| **AVRC** | AIDS Vaccine Research Committee |
| **AVRWG** | AIDS Vaccine Research Working Group |
| **BAMBU** | Bacteriology and Mycology Biostatistical Unit |
| **BAMSG** | Bacteriology and Mycology Study Group |
| **BISC** | Bioinformatics Integration Support Contract |
| **BSE** | bovine spongiform encephalopathy |
| **BSL-3** | biosafety level three |
| **BTEP** | BioTechnology Engagement Program |
| **CASG** | Collaborative Antiviral Study Group |
| **CCTAT** | Cooperative Clinical Trials in Adult Kidney Transplantation |
| **CCTPT** | Cooperative Clinical Trials in Pediatric Kidney Transplantation |
| **CDC** | Centers for Disease Control and Prevention |
| **CFS** | chronic fatigue syndrome |
| **cGMP** | **c**urrent **G**ood **M**anufacturing **P**ractices |
| **CIPRA** | Comprehensive International Program for Research on AIDS |
| **CJD** | Creutzfeldt-Jakob disease |
| **CMB** | Contract Management Branch |
| **CMV** | cytomegalovirus |
| **CPCRA** | Terry Beirn Community Programs for Clinical Research on AIDS |
| **CRADA** | Cooperative Research and Development Agreement |
| **CRC** | Cooperative Research Center |
| **CRCA** | Clinical Research Curriculum Award |
| **CRDF** | Civilian Research and Development Foundation |
| **CWD** | chronic wasting disease |
| **DAIDS** | Division of Acquired Immunodeficiency Syndrome, NIAID |
| **DAIT** | Division of Allergy, Immunology and Transplantation, NIAID |
| **DALY** | disability-adjusted life years |
| **DEA** | Division of Extramural Activities, NIAID |
| **DHHS** | U.S. Department of Health and Human Services |
| **DIR** | Division of Intramural Research, NIAID |
| **DMID** | Division of Microbiology and Infectious Diseases, NIAID |
| **DNA** | deoxyribonucleic acid |

| | |
|---|---|
| **EPRU** | Enteric Pathogens Research Unit |
| **FDA** | Food and Drug Administration |
| **FIC** | Fogarty International Center |
| **FY** | fiscal year |
| **GAVI** | Global Alliance for Vaccines and Immunization |
| **GP** | glycoprotein |
| **HAART** | highly active antiretroviral therapy |
| **HBV** | hepatitis B virus |
| **HC CRCs** | Hepatitis C Cooperative Research Centers |
| **HCV** | hepatitis C virus |
| **HIV** | human immunodeficiency virus |
| **HIVNET** | HIV Network for Prevention Trials |
| **HLA** | human leukocyte antigen |
| **HOPE** | Health Omnibus Programs Extension |
| **HPTN** | HIV Prevention Trials Network |
| **HSV** | herpes simplex virus |
| **HVDDT** | HIV Vaccine Design and Development Team |
| **HVTN** | HIV Vaccine Trials Network |
| **IBRP** | Introduction to Biomedical Research Program |
| **ICBG** | International Cooperative Biodiversity Groups Program |
| **ICIDR** | International Collaboration in Infectious Disease Research |
| **ICER** | International Center for Excellence in Research |
| **ICs** | Institutes and Centers |
| **ICTDR** | International Centers for Tropical Disease Research |
| **IDF** | Immune Deficiency Foundation |
| **IHWG** | International Histocompatibility Working Group |
| **IL** | interleukin |
| **IOM** | Institute of Medicine |
| **IPCP** | Integrated Preclinical/Clinical Development Program |
| **ITN** | Immune Tolerance Network |
| **ITREID** | International Training and Research in Emerging Infectious Diseases |
| **JDRF** | Juvenile Diabetes Research Foundation International |
| **LBRF** | louse-borne relapsing fever |
| **LCI** | Laboratory of Clinical Investigation |
| **LGT** | Langat |
| **LPD** | Laboratory of Parasitic Diseases |
| **LUAT** | Lyme urine antigen test |
| **MADGC** | Multiple Autoimmune Disease Genetics Consortium |
| **MDR-TB** | multi-drug-resistant tuberculosis |
| **MERIT** | Method to Extend Research in Time Award |

| | |
|---|---|
| **MHC** | major histocompatibility complex |
| **MIM** | Multilateral Initiative on Malaria |
| **MOU** | Memorandum of Understanding |
| **MRSA** | methicillin-resistant *Staphylococcus aureus* |
| **MRTC** | Malaria Research and Training Center |
| **MSG** | Mycoses Study Group |
| **Mtb** | *Mycobacterium tuberculosis* |
| **MVA** | modified vaccinia virus Ankara |
| **MVDU** | Malaria Vaccine Development Unit |
| **MVI** | Malaria Vaccine Initiative |
| **NAAIDC** | National Advisory Allergy and Infectious Diseases Council |
| **NARAC** | North American Rheumatoid Arthritis Consortium |
| **NARSA** | Network on Antimicrobial Resistance in *Staphylococcus aureus* |
| **NCI** | National Cancer Institute |
| **NCICAS** | National Cooperative Inner-City Asthma Study |
| **NCRR** | National Center for Research Resources |
| **NHIS** | National Health Interview Survey |
| **NIAID** | National Institute of Allergy and Infectious Diseases |
| **NICHD** | National Institute of Child Health and Human Development |
| **NIDDK** | National Institute of Diabetes and Digestive and Kidney Diseases |
| **NIEHS** | National Institute of Environmental Health Sciences |
| **NIGMS** | National Institute of General Medical Sciences |
| **NIH** | National Institutes of Health |
| **NRSA** | National Research Service Award |
| **NVPO** | National Vaccine Program Office |
| **OAS** | Office of Administrative Services, NIAID |
| **OCPL** | Office of Communications and Public Liaison, NIAID |
| **OCR** | Office of Clinical Research, NIAID |
| **OD** | Office of the Director, NIAID |
| **OE** | Office of Ethics, NIAID |
| **OFM** | Office of Financial Management, NIAID |
| **OHRM** | Office of Human Resources Management, NIAID |
| **OPA** | Office of Policy Analysis, NIAID |
| **OSPRT** | Office of Special Populations and Research Training, NIAID |
| **OTD** | Office of Technology Development, NIAID |
| **OTIS** | Office of Technology Information Systems, NIAID |
| **OTT** | Office of Technology Transfer, NIH |
| **PACTG** | Pediatric AIDS Clinical Trials Group |
| **PID** | pelvic inflammatory disease |
| **PIV** | parainfluenza virus |
| **PR** | protease |
| **PRP** | polyribosylribose phosphate |

| | |
|---|---|
| **PrP** | prion protein |
| **R&D** | research and development |
| **RFA** | request for applications |
| **RML** | Rocky Mountain Laboratories |
| **RNA** | ribonucleic acid |
| **RPAB** | Referral and Program Analysis Branch, DEA, NIAID |
| **RSV** | respiratory syncytial virus |
| **RT** | reverse transcriptase |
| **SAIC** | Science Applications International Corporation |
| **SBIR** | Small Business Innovation Research |
| **SBTT** | Small Business Technology Transfer |
| **SCID** | severe combined immunodeficiency disease |
| **SIV** | simian immunodeficiency virus |
| **SLE** | systemic lupus erythematosus |
| **SMART** | Strategies for Management of Anti-Retroviral Therapies |
| **SPR** | Summer Program Review |
| **SRP** | Scientific Review Program |
| **STD** | sexually transmitted disease |
| **STTR** | Small Business Technology Transfer |
| **TB** | tuberculosis |
| **TBEV** | tick-borne encephalitis virus |
| **TDRU** | Tropical Disease Research Unit |
| **TEAC** | Technology Evaluation Advisory Committee |
| **TMRC** | Tropical Medicine Research Center |
| **TSE** | transmissible spongiform encephalopathy |
| **USJCMSP** | U.S.-Japan Cooperative Medical Science Program |
| **VAP** | Vaccine Action Program |
| **VDF** | Vaccine Development Facility |
| **VRC** | The Dale and Betty Bumpers Vaccine Research Center |
| **VRE** | vancomycin-resistant enterococci |
| **VTEU** | Vaccine and Treatment Evaluation Unit |
| **WHO** | World Health Organization |
| **WPR** | Winter Policy Retreat |

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